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PAIN MANAGEMENT 101: A PRIMER FOR
THE BEGINNER

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Pain Management 101: A Primer for the Beginner

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LESSON OBJECTIVES

1. Describe the “Pain Experience”
2. Identify the categories of pain
3. Summarize the key conclusions on the efficacy of intraspinal drug therapy for postoperative pain
4. Discuss the effects of chronic pain on the patient and society
5. List and discuss the difference between primary analgesics and adjuvant analgesics
6. Discuss the risks and benefits of chronic opioid therapy
7. Explain the role universal precautions for chronic opioid therapy in reducing the risks associated with chronic opioid therapy
8. Compare and contrast the tricyclic antidepressants and the serotonin and norepinephrine reuptake inhibitors when used to treat chronic pain
9. Discuss the limitations of the centrally acting muscle relaxants for the treatment of chronic pain
10. Discuss non-pharmacologic therapies used to treat chronic pain

INTRODUCTION

Pain is the most common reason that patients seek medical attention yet the undertreatment of acute and chronic pain persists despite decades of efforts to provide clinicians with information about analgesics. Consequences of unrelieved acute pain range from deleterious effects on the cardiac, gastrointestinal and pulmonary systems to the development of chronic pain syndromes. Therefore, the anesthesiologist is in a position to make a significant difference in long term patient outcome. The major impact of pain on patient health is staggering and begins in the operating room and extends well into the postoperative period. This lesson will review the pathophysiology of pain and the management of acute and chronic pain.
PHYSIOLOGY OF PAIN PERCEPTION

The Pain Experience

The “Pain Experience” involves three components: 1) sensory/discriminative, 2: affective/emotional and 3) evaluative/cognitive.

The sensory/discriminative component of pain provides information on the intensity location and quality of the pain. These pathways consist of peripheral receptor activation, axon depolarization, and ascending pathways to the cortex for processing.

The ascending pathways that carry impulses from the nociceptor to the sensory cortex also give off fibers to brainstem structures and deep brain structures such as the limbic system and periaqueductal grey. Activation of the structures in the brainstema and deep brain will stimulate emotional and sympathetic responses from the individual leading to the emotional/affective component of pain.

Finally, ascending pain pathways also send projections to the forebrain structures where the pain is processed on a cognitive and evaluative level explaining why patients respond differently to pain based on culture, gender, and past experiences.

The main neurotransmitter in primary afferents is the excitatory amino acid glutamate. Activation of nociceptors causes the release of glutamate from central terminals; this release acts on the ionotropic glutamate receptor amino-3-hydroxy-5-methylisoxazole 4-propionic acid postsynaptically to cause a rapid depolarization of dorsal horn neurones and, if threshold is reached, action potential discharge.

Pain Classification

Pain can be mechanistically divided into 4 classifications: nociceptive, inflammatory, functional and neuropathic. Nociceptive pain is the transient pain in response to a noxious stimulus that activates high threshold afferents. Nociceptive pain serves a protective function. Inflammatory pain is the spontaneous and hypersensitivity to pain in response to tissue damage and inflammation (i.e. postoperative pain, trauma, arthritis). Functional pain is hypersensitivity to pain resulting from abnormal central processing of normal input (i.e. pathological irritable bowel syndrome, fibromyalgia). Neuropathic pain is the spontaneous pain and hypersensitivity to pain in association with damage to or lesion of the nervous system (i.e. peripheral neuropathy, post herpetic neuralgia).

The efficacy of analgesics is dependent upon the pain classification. The primary analgesics are more efficacious in nociceptive and inflammatory pain whereas the adjuvant agents are more efficacious in neuropathic and functional pain. Each pain classification involves different pain mechanisms and within each classification, there are multiple different pain mechanisms. This concept has been verified through multicenter randomized controlled trials in new novel agents that led to FDA approval for specific pain syndromes. A more detailed discussion on these agents will follow below.
Table 1 Pain Classification

<table>
<thead>
<tr>
<th>Classification</th>
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<tbody>
<tr>
<td>Nociceptive Pain</td>
</tr>
<tr>
<td>Neuropathic Pain</td>
</tr>
<tr>
<td>Inflammatory Pain</td>
</tr>
<tr>
<td>Functional Pain</td>
</tr>
</tbody>
</table>

POSTOPERATIVE PAIN MANAGEMENT

Acute pain is defined as pain that arises from tissue injury that is expected to resolve once the patient recovers from the injury. The most common type of acute pain is postoperative pain. Although we have many effective modalities for the treatment of postoperative pain, many patients suffer needlessly from under treatment of their pain postoperatively.

Preoperatively, a discussion should take place with the patient on the different options for postoperative pain control. Options for postoperative pain control include 1) intravenous patient controlled analgesia, 2) intermittent oral, IV, or IM analgesics, 3) epidural or intrathecal analgesia. If the patient has preexisting pain, special attention should be given to the current medications as some will affect the postoperative treatment of pain. If the patient is on an NSAID, it should be stopped at least 24 hours prior to surgery. Aspirin should be stopped 7 days prior to surgery. The new COX-2 inhibitors do not need to be discontinued. If the patient is taking an opioid, every effort should be made to wean the opioid to reverse the tolerance the patient may have. However, it may not be possible to wean the opioid because of severe pain. In this case, a preoperative pain consult should be considered. Figure 1 and 2 summarize an algorithm for the management of acute postoperative pain in the adult undergoing major or minor surgery. Table 2 summarizes suggested dosing for intravenous patient controlled analgesia.
Figure 1

**ADULT MAJOR SURGERY**
*(Intravenous Patient Controlled Analgesia)*

1. **Mucous Spasms?**
   - Yes: Add Muscle Relaxant
   - No: IV PCA Hydromorphone

2. **Pain Persisting or Increasing?**
   - Yes: Add NSAID
   - No: Evaluate comorbidities, consider adjuvant

3. **Pain Persisting or Increasing**
   - Yes: Go to adult minor surgery algorithm
   - No: Continue Current Rx

4. **Pain Persisting or Increasing**
   - Yes: Continued edema NSM IV hydrocortisone intake 50 mg q 8 hrs tapered over 2-4 weeks
   - No: Distributed edema NSM IV hydrocortisone intake 50 mg q 6 hrs tapered over 2-4 weeks

5. **Pain Persisting or Increasing**
   - Yes: IV PCA Hydromorphone
   - No: Pain Persisting or Increasing

6. **Pain Persisting or Increasing**
   - Yes: Change to Morphine 15-30 mg q 4 hrs tapered over 2-4 weeks
   - No: Pain Persisting or Increasing

7. **Pain Persisting or Increasing**
   - Yes: Change to Hydrocodone 5-10 mg po q 4 hrs tapered over 2-4 weeks
   - No: Pain Persisting or Increasing

8. **Pain Persisting or Increasing**
   - Yes: Anosmia or comorbidity, consider adjuvant
   - No: Pain Persisting or Increasing

9. **Pain Persisting or Increasing**
   - Yes: Go to major surgery algorithm
   - No: Pain Persisting or Increasing

10. **Pain Persisting or Increasing**
    - Yes: Refer to Pain Specialist
    - No: Pain Persisting or Increasing

*For major surgery, the on demand intermittent clinician administration of analgesics is not recommended.

Figure 2

ADULT MINOR SURGERY

1. **Mucous Spasms?**
   - Yes: Add Muscle Relaxant
   - No: IV PCA Morphine

2. **Pain Persisting or Increasing**
   - Yes: Add NSAID
   - No: Evaluate comorbidities, consider adjuvant

3. **Pain Persisting or Increasing**
   - Yes: Hydrocodone + acetaminophen (Vicodin) or Codeine + acetaminophen
   - No: Pain Persisting or Increasing

4. **Pain Persisting or Increasing**
   - Yes: Add NSAID
   - No: Pain Persisting or Increasing

5. **Pain Persisting or Increasing**
   - Yes: Change to Morphine 15-30 mg po q 4 hrs tapered over 2-4 weeks
   - No: Pain Persisting or Increasing

6. **Pain Persisting or Increasing**
   - Yes: Change to Hydrocodone 5-10 mg po q 4 hrs tapered over 2-4 weeks
   - No: Pain Persisting or Increasing

7. **Pain Persisting or Increasing**
   - Yes: Go to Major Surgery Algorithm
**TABLE 2 – Intravenous Patient Controlled Analgesia Guidelines**

<table>
<thead>
<tr>
<th></th>
<th>Morphine</th>
<th>Hydromorphone</th>
<th>Fentanyl</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>1 mg</td>
<td>0.2 mg</td>
<td>20 mcg</td>
</tr>
<tr>
<td><strong>Lockout</strong></td>
<td>10 minutes</td>
<td>10 minutes</td>
<td>10 minutes</td>
</tr>
<tr>
<td><strong>Loading Dose</strong></td>
<td>2 mg</td>
<td>0.4 mg</td>
<td>40 mcg</td>
</tr>
<tr>
<td><strong>Clinician Dose</strong></td>
<td>2 mg/hour prn</td>
<td>0.4 mg/hour prn</td>
<td>40 mcg/hour prn</td>
</tr>
<tr>
<td><strong>Continuous Infusion</strong></td>
<td>Not Recommended When Initiating the IVPCA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Intraspinal therapies for postoperative pain**

It is beyond the scope of this article to go into details of intraspinal therapies for postoperative pain management; therefore, key points will be summarized about the safety and efficacy of this technique. There is a vast amount of literature on the efficacy of intrathecal and epidural agents for postoperative pain.

Single shot intrathecal opioids are commonly used to treat postoperative pain with some conflicting studies on efficacy. For hydrophilic opioids such as morphine and hydromorphone, the studies generally show: 1) a slower onset of analgesia as compared to epidural delivery; 2) a decrease in systemic opioid requirements; 3) dose dependent side effects with the optimum dose in the range of 0.1 -0.3 mg for morphine; and 4) no clear cut advantage over systemic opioids; however, there is likely an advantage to add to a spinal anesthetic. In contrast intrathecal lipid soluble opioids such as fentanyl* and sufentanil* show a faster onset of action as compared to hydrophilic opioids, and there is a lower incidence of side effects. The optimum dose for fentanyl* and sufentanil* is 25-40 mcg and 15-1.75 mcg respectively.

There have been numerous studies on the efficacy and safety of epidural hydrophilic and lipophilic opioids delivered as a single shot and continuous infusion. Whereas studies on the use of epidural morphine for thoracic and upper abdominal surgery show conflicting results, the epidural delivery of morphine for lower abdominal and orthopedic surgery consistently show superior results over systemic opioids. Single bolus epidural morphine has been demonstrated to have an analgesic duration of up to 24 hours. There are very few studies comparing single bolus vs continuous infusion of epidural morphine. One study showed that a single bolus of morphine was no different than a continuous infusion of epidural morphine for up to 12 hours after laparoscopic cholecystectomy. This suggests that a continuous catheter should be used for patients that require pain control for more than 24 hours. If less than 24 hours is required, a single shot dose is sufficient. Given the different mechanism of action, it is a reasonable assumption that the addition of a local anesthetic to an opioid is better than either alone. Studies have supported this assumption with the opioid/local anesthetic combination being superior to opioid alone and local anesthetic alone in thoracic, upper abdominal, lower abdominal and hip/knee surgery.
Another area of controversy is the difference between the lumbar and thoracic delivery of epidural opioids for thoracic and upper abdominal surgery. Studies using morphine and fentanyl have very different results. For morphine, studies have shown that 1) after thoracotomy, the thoracic delivery results in a faster onset of analgesia and lower total dose of morphine required for satisfactory analgesia and 2) after upper abdominal surgery, there is no difference in outcome. These differences are likely due to the much larger spinal cord segmental innervation for upper abdominal surgery versus thoracic surgery requiring more spinal segmental effect of the morphine for analgesia. Numerous studies using epidural fentanyl* in thoracotomy patients have failed to show any difference in analgesia with lumbar versus thoracic delivery. These studies suggest that the analgesia resulting from the systemic absorption of the lipophilic agents outweighs the spinal effect. Table 3 summarizes the conclusion on the efficacy of epidural opioids in postoperative pain.

Preemptive Analgesia

There have been numerous studies on the preemptive effect of the NSAIDs on postoperative pain with conflicting results. A review of 20 trials comparing preincisional with postincisional NSAID or acetaminophen using a parallel or crossover design found some aspects of postoperative pain control were improved by preemptive treatment in only 4 of the 20 trials. Overall the data demonstrated preemptive NSAIDs to be of no analgesic benefit when compared to postincisional administration. Another review of 12 randomized controlled trials of preincisional versus postincisional NSAIDs showed that 6 trials favored preincisional and 6 found no difference for pain relief. As a supplemental analgesic in these trials, preincisional NSAIDs were significantly better than postincisional.

Since the NSAIDs can cause a decrease in platelet aggregation and an increase in bleeding time, they may increase the risk of perioperative bleeding. Increased perioperative bleeding with ketorolac has been observed and is currently contraindicated for use as a preemptive analgesic. The COX-2 inhibitors do not interfere with platelet aggregation or bleeding time and do not cause increased perioperative bleeding; therefore, they should be considered for preemptive analgesia and perioperative use. Unfortunately, studies that showed a positive affect of the COX-2 inhibitors on postoperative pain have been removed from the literature after it was discovered that the data was fraudulent.

Table 3 - Epidural Opioids for Postoperative Pain: Conclusions

- Clear advantage of epidural opioids in lower abdominal and lower extremity surgery. Questionable advantage in upper abdominal and thoracic surgery.
- No clear advantage of a continuous epidural infusion of opioid over single dose in first 24 hours. Clear advantage beyond 24 hours.
- Clear advantage of opioid/local anesthestic combo in all types of surgery.
- Clear advantage of thoracic over lumbar delivery of hydrophilic opioid for thoracotomy but not upper abdominal surgery. For lipophilic agents, no difference.
CHRONIC PAIN MANAGEMENT

Living with chronic pain has deleterious effects on many aspects of the patient’s daily life. These effects include deterioration in physical functioning, the development of psychological distress and psychiatric disorder, and impairments in interpersonal functioning. For example, approximately 40% of patients with chronic pain also experience major depression.

The interpersonal consequences of chronic pain are also clear. Marriages and other family relationships may suffer when an individual who is in pain is not able to be active in the relationship or feels depressed or anxious. Intimacy is not usually discussed in patient-physician relations, but intimacy in a relationship can change dramatically when a partner has chronic pain.

In addition to the personal suffering it causes, chronic pain imposes a burden on society in increased healthcare costs, disability, and lost workdays. Because of the complex nature of chronic pain on mental and physical functioning, a multidisciplinary approach to treatment is often required. Because it is beyond the scope of this article to cover all aspects of pain medicine, the focus will be on the pharmacologic approach.

Table 4 – Effects of Chronic Pain on the Patient and Society

<table>
<thead>
<tr>
<th>Physical Functioning</th>
<th>Psychological Morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Ability to perform activities of daily living</td>
<td>• Depression (most common)</td>
</tr>
<tr>
<td>• Sleep Disturbance</td>
<td>• Anxiety</td>
</tr>
<tr>
<td></td>
<td>• Anger</td>
</tr>
<tr>
<td></td>
<td>• Loss of self-esteem</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Social Consequences</th>
<th>Societal Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Relationship with family and friends</td>
<td>• Healthcare costs</td>
</tr>
<tr>
<td>• Intimacy/sexual activity</td>
<td>• Disability</td>
</tr>
<tr>
<td>• Social isolation</td>
<td>• Lost workdays</td>
</tr>
</tbody>
</table>

Pharmacological treatment of Chronic Pain

Pain is mediated through both peripheral and central mechanisms. In an acute trauma, peripheral nociceptors are stimulated and transmit pain signals to the dorsal horn of the spinal cord and ultimately to the thalamus and the cortex. In the normal pain response, pain intensity increases as the stimulus intensity increases. There are various sites along the pain pathway where analgesics exert their activity. Thus, in theory, the use of two or more agents with differing mechanisms or multiple modes of analgesia (ie, epidural analgesia and NSAIDs) increases the likelihood of interrupting pain signals and relieving pain. Evidence suggests that COX-2 is induced in both the peripheral and central nervous systems in response to pain, thus suggesting that COX-2 inhibitors and NSAIDs capable of CNS penetration may provide pain relief via inhibition of central COX-2 induction in addition to their peripheral actions at the site of injury.
Pharmacologic agents for the management of chronic pain are divided into primary analgesics which have intrinsic analgesic properties and adjunct analgesics which may have primary analgesic properties in neuropathic pain but usually enhance the analgesic effects of primary analgesics when used in non neuropathic pain syndromes. Table 5 summarizes these agents.

**TABLE 5 - Analgesic options to treat chronic pain**

<table>
<thead>
<tr>
<th>Primary Analgesics</th>
<th>Adjunct Analgesics</th>
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</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>Tricyclic antidepressants</td>
</tr>
<tr>
<td>NSAIDs/COX-2 inhibitors</td>
<td>Serotonin/Norepinephrine Reuptake Inhibitors</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Anticonvulsants</td>
</tr>
<tr>
<td>Opioids</td>
<td>Muscle relaxants</td>
</tr>
<tr>
<td></td>
<td>Topical agents</td>
</tr>
</tbody>
</table>

**Acetaminophen**

The mechanism of action of acetaminophen is unclear but it is thought to inhibit COX-3 which is a cyclooxygenase – 1 variant. Cyclooxygenase (COX) isoenzymes are known to catalyze the rate-limiting step of prostaglandin synthesis and are targets of the nonselective NSAIDs.

**NSAIDs and COX-2 inhibitors**

Nonsteroidal anti-inflammatory drugs are nonselective inhibitors of COX – 1 and COX – 2. This results in a decrease in the synthesis of prostaglandins from arachidonic acid leading to a reduction in pain and inflammation. COX – 1 is constitutively present in most tissues and leads to the synthesis of prostaglandins that regulate physiologic processes most important in gastric mucosa, kidneys, platelets and vascular endothelium. COX – 2 is inducible in most tissues, mainly at sites of inflammation by cytokines; however, it is constitutively expressed in the brain and kidneys. COX – 2 results in the synthesis of
prostaglandins that mediate inflammation, pain and fever. Upon trauma or injury, arachadonic acid is converted by (COX)-2 to prostaglandins (PGs) at the site of injury. PGs sensitize the peripheral nociceptors to heighten sensitivity at the site of injury, causing primary hyperalgesia or increased sensitivity to pain. Recent data support the concept that PGs and COX also mediate pain centrally, and that a humoral response is in part responsible for the transmission of the pain signal into the CNS. Interleukin-1beta is increased in the spinal column after tissue injury, causing an upregulation of COX-2. Vascular cells expressing mRNA for COX-2 have a coupled system to produce PGE$_2$, primarily in the dorsal horn of the spinal column. PGE$_2$ facilitates nociceptive transmission in the spinal cord, resulting in central sensitization. The increase in sensory outflow causes a heightened pain awareness and spread of pain beyond the injury site. Therefore, inflammation following tissue injury results in increased sensitivity at the location of injury (peripheral sensitization) and increased sensitivity that spreads beyond the injury site (central sensitization). Prostaglandins play an important role in these processes. Unlike the COX – 1 inhibitors, the COX – 2 inhibitors have minimal effect on the gastric mucosa and platelet function; however, both COX – 1 and COX – 2 inhibitors may affect kidney function. In addition, the COX – 2 inhibitors have been implicated in an increase risk of cardiovascular events. This may be due to the importance of COX – 2 in ischemic protection.

**Tramadol**

Tramadol is a weak mu opioid agonist and a norepinephrine and serotonin reuptake inhibitor with both mechanisms associated with analgesia. Tramadol is initiated at 50 mg twice a day and titrated up to 400 mg/ day divided four times per day. Most patients will achieve analgesia at 250 mg/day. Randomized placebo controlled trials have demonstrated tramadol to be effective in fibromyalgia and diabetic peripheral neuropathy. An extended release once a day preparation is available. Common side effects include nausea, dizziness, and somnolence. Serotonin syndrome has been reported in combination with MAO inhibitors and Serotonin Specific Reuptake inhibitors. In addition it has been reported to lower seizure threshold and should be used with caution in patients with seizure disorders. Although it has a low abuse potential, there may be an increased risk of addiction in patients with a history of substance abuse.

**Opioids**

The opioids act on peripheral and central mu, kappa, and delta opioid receptors. Activation of presynaptic mu receptors inhibits calcium influx resulting in lowered neurotransmitter release. Activation in postsynaptic mu receptors results in an increase in potassium conductance resulting in a stabilization of the postsynaptic membrane. Stimulation of supraspinal mu receptors activates descending inhibitory pathways that modulate transmission in the spinal cord. In addition, the opioids alter limbic system activity.

Numerous studies have demonstrated the efficacy of the opioids in a variety of chronic pain states including neuropathic and non-neuropathic. However studies documenting the long-term efficacy, however, have not been conducted. Chronic opioid therapy to treat chronic pain remains controversial. Over the centuries, the pendulum has swung back and forth with regard to the use of the opioids to treat pain. In the mid 20th century, opioids were
limited due to fears of addiction and diversion and the late 20\textsuperscript{th} century, the pendulum went to the other side with liberal use to treat chronic pain. With the turn of the 21\textsuperscript{st} century the pendulum is moving back toward the middle with the recognition of the importance of the opioids in chronic pain management but the understanding of the need to balance these benefits with risks. Recently published guidelines acknowledge that opioid analgesics have an important role in pain management and that under use of these agents may contribute to suboptimal pain management. However, these guidelines also acknowledge that the abuse of prescription opioids has become an epidemic, with dramatic increases seen in the United States. A set of universal precautions have therefore been developed as a guide to help the physician who prescribes opioids. See Table 6

<table>
<thead>
<tr>
<th>Table 6 Universal Precautions for Chronic Opioid Use to Treat Pain</th>
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<tbody>
<tr>
<td>1. Diagnosis with appropriate differential</td>
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<tr>
<td>2. Psychological assessment, including risk of addictive disorders</td>
</tr>
<tr>
<td>3. Informed consent</td>
</tr>
<tr>
<td>4. Treatment agreement</td>
</tr>
<tr>
<td>5. Pre- and Post-intervention assessment of pain level and function</td>
</tr>
<tr>
<td>6. Appropriate trial of opioid therapy with/without adjunctive medication</td>
</tr>
<tr>
<td>7. Reassessment of pain score and level of function</td>
</tr>
<tr>
<td>8. Regularly assess the “4 A’s” (Analgesia, Activities of daily living, Adverse effects, Aberrant drug-taking behaviors)</td>
</tr>
<tr>
<td>9. Periodically review pain diagnosis and comorbid conditions, including addictive disease</td>
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<tr>
<td>10. Documentation</td>
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Before considering initiation of opioid treatment, it is important for the physician, patient, and family to understand the distinction between physical dependence, tolerance, and addiction. Physical dependence is a pharmacologic effect characterized by the development of a withdrawal syndrome when an opioid drug is discontinued, when the dose is substantially reduced, or if an antagonist is administered. Dependence occurs in almost all patients on opioids, and does not connote addiction. Tolerance means that a greater amount of drug is needed over time to maintain a therapeutic effect. The number of patients who develop clinically relevant tolerance is unknown. Tolerance may also occur to side effects, and thus may be beneficial. Some patients who develop tolerance can have their pain managed by judicious dose increases; others who develop inexorable tolerance cannot have their pain managed by opioids. There is no evidence to support a role for analgesic tolerance in the development of drug addiction. Addiction is, however, often (though not always) associated with tolerance. Addiction is a psychiatric disorder consisting of continued, compulsive use of the substance despite harm. The Diagnostic and Statistical Manual of Mental Disorders provides nine categories of opioid use or opioid-induced disorders, including diagnostic criteria for opioid dependence or opioid abuse. True addiction (patient loss of control) may become obvious only when the physician stops prescribing the medicine. There is, however, little evidence that addiction is common within the chronic pain population. In a study reviewing the available data, it was found that prevalence estimates for addiction in patients with chronic pain ranged from 3\% to 19\%.
After conservative treatments, including nonopioids, have failed to control the patient’s pain, an opioid should be considered. In general, a short-acting weak opioid such as hydrocodone or codeine should be used first. If the patient is requiring more than 3-4 short acting weak opioid/day, consider converting to a long-acting opioid. Controlled-release or long-acting opioids not only provide convenience to patients by reducing the number of daily doses required, but they also provide a pharmacokinetic profile that results reduced serum level peaks and troughs, and thereby an improvement in the consistency of effective analgesia and a potential to reduction in opioid-related side effects that are often correlated with high peak serum levels. When converting to a long-acting opioid, access to a short-acting opioid for breakthrough pain should be limited. Evaluation by a pain specialist may be considered when the morphine equianalgesic dosages exceed 90 mg/day. The benefits of levels higher than 180 mg/day have not been established. Table 7 lists the side effects of the opioids.

### Table 7 Opioid Side Effects

| 1. | Constipation            |
| 2. | Sedation               |
| 3. | Nausea                 |
| 4. | Neurotoxic effects     |
|   | a. Delerium            |
|   | b. Hyperalgesia        |
| 5. | Respiratory depression |
|   | a. Low risk in ambulatory patients taking opioids at recommended starting doses |
| 6. | Other effects          |
|   | a. Decreased testosterone |
|   | b. Decreased immunity |

**Pregabalin and Gabapentin**

Pregabalin and gabapentin both bind to the alpha – 2 – delta subunit of volatage gated calcium channels located on the presynaptic terminal of C fibers in the dorsal horn cells. This binding reduces calcium influx during depolarization resulting in a reduction of the release of neurotransmitters such as glutamate and substance P. Unlike the opioids, which limit calcium influx via a G-protein pathway, there is no tolerance associated with pregabalin and gabapentin. There are several major differences between these two agents. First, pregabalin has linear kinetics with > 90% bioavailability at all doses whereas gabapentin is nonlinear. Gabapentin 900 mg has a 60% bioavailability and a 3600 mg dose has only 33% bioavailability. Second, the time to effective dose is usually 1-2 days for pregabalin and 10-14 days for gabapentin. Third, pregabalin is a scheduled V drug due to reports of euphoria and mild withdrawal symptoms with addiction studies. However, clinical experience has shown that the abuse potential is extremely low.

Pregabalin and gabapentin are FDA approved for the treatment of postherpetic neuralgia. Only pregabalin is FDA approved for painful diabetic peripheral neuropathy and fibromyalgia. However, clinical experience suggests that both agents are effective in a wide
range of neuropathic pain syndromes. In addition to the reduction in pain associated with these agents, all studies have demonstrated a significant improvement in sleep disturbances. The most common side effect with these agents is sedation, dizziness, cognitive impairment and weight gain.

**Tricyclic Antidepressants (TCAs)**

The TCAs exert relief of pain through serotonin and norepinephrine reuptake blockade. It is thought that the norepinephrine reuptake inhibition leads to pain relief more than serotonin reuptake inhibition as the selective serotonin reuptake inhibitors have resulted in inconsistent analgesia in controlled trials. Other potential analgesic mechanisms include blockade of alpha adrenergic receptors, sodium and potassium channel modulation, modulation of monoamine neurotransmitters and possible NMDA-receptor antagonism.

There are many randomized controlled trials and meta-analyses that have demonstrated the benefit of the TCAs in postherpetic neuralgia and painful diabetic peripheral neuropathy. However, the onset is delayed (often 4-8 weeks of therapy required before onset) and there are many side effects related to the anticholinergic effects. In addition, weight gain can be a problem. It is recommended that these agents be started low and titrated slowly over 4-8 weeks. At least 4 weeks at the maximum tolerated dose are required for a fair trial.

**Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)**

As with the TCA, the SNRIs (duloxetine, milnacipram, and venlafaxine) provide analgesia through the inhibition of serotonin and norepinephrine reuptake. However, these agents have much lower anticholinergic effects resulting in a better tolerability. In addition, duloxetine has a much faster onset with pain relief occurring within the first week of therapy.

Duloxetine is FDA approved for the treatment of painful diabetic neuropathy and fibromyalgia. It also has pending approval for the treatment of osteoarthritis and back pain and may receive a general chronic pain indication. Milnacipram is FDA approved for the treatment of fibromyalgia. Venlafaxine* does not have an approved pain indication. The most common side effects with the SNRI is nausea which can be minimized by starting at a lower dose and titrating.

**5% Lidocaine Patch**

Lidocaine patch is a pliable patch with a mild adhesive that contains 5% lidocaine. The patch is FDA approved for the treatment of postherpetic neuralgia. When applied, the lidocaine penetrated the skin to reach sodium channels on free nerve endings resulting in a membrane stabilization. Analgesia, but no anesthesia is produced, which suggests that the patch affects abnormal nerves but not normally functioning nerves. This theory is based on the observation that injured nerves have an increase in the number of sodium channels that may lower the threshold for firing. The lidocaine patch may bring the balance to a more normal level.
Lidocaine patch has an excellent safety and tolerability profile. The only adverse events are mild skin reactions, erythema or rash. There is minimal system absorption with non-detectable plasma lidocaine levels with up to 4 patches applied.

**Centrally Acting Muscle Relaxants**

Centrally acting muscle relaxants are clinically indicated for acute pain with associated muscle spasms. The chronic use of these agents is controversial and should be limited to selected cases. Centrally acting, skeletal muscle relaxants are commonly used for the treatment of painful musculoskeletal conditions associated with muscle spasms, such as acute low back pain and muscle strains. Drugs falling in this class are structurally unrelated compounds that may indirectly relax skeletal muscle by blocking polysynaptic neurons in the spinal cord and descending reticular formation in the brain.

There is minimal data on the clinical efficacy of the muscle relaxants in chronic pain. One study demonstrated a significant benefit of cyclobenzaprine over placebo in fibromyalgia. However, cyclobenzaprine has a structure similar to the TCAs which may explain the positive effects in the pain syndrome. Other studies using the TCAs in fibromyalgia have also been positive. The muscle relaxants have many side effects that limit chronic use. Table 8 lists the common side effects.

**Table 8 Side effects of the Centrally Acting Muscle Relaxants**

<table>
<thead>
<tr>
<th>1. CNS side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Sedation</td>
</tr>
<tr>
<td>b. Dizziness</td>
</tr>
<tr>
<td>c. Confusion</td>
</tr>
<tr>
<td>d. Blurred vision</td>
</tr>
<tr>
<td>2. Potential for abuse with carisoprodal (Schedule IV)</td>
</tr>
<tr>
<td>3. GI side effects</td>
</tr>
<tr>
<td>a. Nausea</td>
</tr>
<tr>
<td>b. Epigastric distress</td>
</tr>
<tr>
<td>c. Vomiting</td>
</tr>
<tr>
<td>4. Anticholinergic side effects</td>
</tr>
<tr>
<td>a. Dry mouth</td>
</tr>
<tr>
<td>b. Urinary retention</td>
</tr>
</tbody>
</table>

**Nonpharmacologic Therapies for the Treatment of Chronic Pain**

Nonpharmacologic therapies are an important part of chronic pain treatment and should be considered in all patients. Transcutaneous Electrical Nerve Stimulation (TENS) uses electrical stimulation of the skin to relieve pain by interfering with the neural transmission of signals from underlying pain receptors. Three controlled studies showed that 66% of the patients experienced immediate symptomatic improvement and 44% maintained the improvement for 1 year. Acupuncture uses small needles placed in body areas associated with
specific areas of the nervous system. It is thought that this stimulates the release of centrally acting analgesics such as the endorphins and the endocannabinoids. Many studies have demonstrated a positive effect on pain however; the duration is usually short lived requiring repeated treatments. Massage has been shown to relieve pain but his generally recommended that more active physical therapies and aerobic exercises be encouraged for chronic pain patients.

Psychological therapies may be indicated for patients with psychological comorbidities and who are open to these techniques. Biofeedback uses monitoring devices to furnish information regarding an autonomic bodily function, such as heart rate or blood pressure, in an attempt to gain some voluntary control over that function. It is often used in combination with relaxation techniques. Cognitive behavioral therapy uses education linked to therapy to help the chronic pain patients gain more control over their lives. It teaches them to control their pain and not let the pain control them.

**SUMMARY**

Recent evidence supports the multimodal analgesia techniques for the management of both acute and chronic pain. For acute pain, use a regional analgesic technique whenever possible. When using systemic opioids for postoperative pain, the addition of a COX-2 inhibitor may have opioid sparing effects.

Chronic pain has multifactorial effects on the continuum of depression/anxiety, functional impairment, and sleep disturbances. Rational polypharmacy is often required in which multiple drugs with different mechanisms may be required. When using the opioids, a risk assessment is required with periodic re-assessment to maximize the benefits and minimize the risks. A better understanding of pain mechanisms and drug pharmacology allows for a rational choice of analgesics and their combinations.

**Bibliography**

4. Loeser JD. Bonica’s Management of Pain. Lippincott Williams and Williams, 2001 (This is the bible of clinical pain management. A 2010 edition is soon to be released)


8. Wallace MS, Staats P. Pain Medicine and Management: Just the Facts, McGraw Hill Co, Inc. New York, New York, 2005. (This is a good board review book)
### Summary of Generic and Trade Names

<table>
<thead>
<tr>
<th>Category</th>
<th>Medication</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonin Norepinephrine Reuptake Inhibitors</td>
<td>Duloxetine</td>
<td>Cymbalta®</td>
</tr>
<tr>
<td></td>
<td>Milnacipram</td>
<td>Savella®</td>
</tr>
<tr>
<td></td>
<td>Venlafaxine</td>
<td>Effexor®</td>
</tr>
<tr>
<td>Opioids</td>
<td>Tramadol</td>
<td>Ultram®, Ultracet®</td>
</tr>
<tr>
<td></td>
<td>Hydrocodone</td>
<td>Vicodin®, Norco®, Lorcet®, Lortab®</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Gabapentin</td>
<td>Neurontin®</td>
</tr>
<tr>
<td></td>
<td>Pregabalin</td>
<td>Lyrica®</td>
</tr>
<tr>
<td>Muscle Relaxants</td>
<td>Cyclobenzaprine</td>
<td>Flexeril®</td>
</tr>
<tr>
<td>Topical Agents</td>
<td>5% lidocaine patch</td>
<td>Lidoderm®</td>
</tr>
</tbody>
</table>
Key Phrases

1. Pain physicians utilize interventions (medications and interventional therapies) to treat the sensory/discriminative (analgesics, nerve blocks) and emotional/affective (antidepressants, anxiolytics) component of pain whereas psychological treatments are directed at the emotional/affective and cognitive evaluative component of the pain experience (section on the pain experience)

2. The best evidence on the effect of epidural analgesia for postoperative pain is with the use of an opioid/local anesthetic combination through a thoracic catheter for thoracotomy or a lumbar catheter for pelvic surgery and lower extremity orthopedic surgery. (section on intraspinal therapies for postoperative pain)

3. Combining drugs with different mechanisms may enhance analgesia and reduce side effects by allowing for lower doses of each drug (end of the second paragraph, pharmacological therapies for chronic pain)

4. For the treatment of chronic non-cancer pain, the opioids should be used after more conservative non-opioids have failed AND a proper risk management evaluation and plan has been documented (at the end of the opioid section)

5. Although many anticonvulsants have been used to treat chronic neuropathic pain, only pregabalin and gabapentin have the most evidence based on placebo-controlled, randomized, double-blind trials. (at the end of the section on pregabalin and gabapentin)

6. The main difference between duloxetine and the tricyclic antidepressants for the treatment of chronic pain is that duloxetine has a faster onset of action and fewer side effects (at the end of the Serotonin and Norepinephrine Reuptake Inhibitors)
TEST QUESTIONS

1. Which of the following is true about the sensory discriminative component of the pain experience?
   a. Involves cortical processing of pain
   b. Only provides information about the quality of the pain
   c. The main purpose is to bring out the emotional aspects of pain
   d. Explains why individuals respond differently to pain based on past experiences and gender.

Answer: a

2. Which of the following statements is true about neuropathic pain?
   a. Transient pain in response to a noxious stimulus that activates high threshold afferents
   b. Spontaneous pain and hypersensitivity to pain in association with damage to or lesion of the nervous system
   c. Spontaneous and hypersensitivity to pain in response to tissue damage and inflammation
   d. Hypersensitivity to pain resulting from abnormal central processing of normal input

Answer: b

3. Which of the following statements is true about postoperative pain control?
   a. Hydrophilic opioids have a faster onset than lipophilic opioids
   b. No clear advantage of epidural opioids in lower abdominal and lower extremity surgery over systemic opioids
   c. Clear advantage of a continuous epidural infusion of opioid over single dose in first 24 hours
   d. Clear advantage of opioid/local anesthetic combo in all types of surgery.

Answer: d

4. What is the most common psychological comorbidity among chronic pain patients?
   a. Anxiety
   b. Depression
   c. Anger
   d. Loss of self esteem

Answer: b
5. Which of the following drugs work the best in neuropathic pain?
   a. Anticonvulsants
   b. Acetaminophen
   c. NSAID
   d. Opioid

Answer: a

6. Which of the following is true about chronic opioid therapy to treat chronic noncancer pain?
   a. The risks have been overstated and their use should be used more liberally
   b. Although guidelines acknowledge the important role of opioids in pain management, they also acknowledge that the abuse of prescription opioids has become an epidemic
   c. Physical dependence on opioids is the same as addiction
   d. When first starting a chronic opioid, a strong long acting opioid should always be used

Answer: b

7. When are “Universal Guidelines” to be used
   a. Only for pediatric pain patients who need opioids
   b. Only for the drug addict who needs opioids to treat pain
   c. For all patients that are started on opioids to treat chronic pain
   d. For all patients who need pain treatment regardless of the drug or therapy used.

Answer: c

8. Which of the following antidepressants has FDA approval to treat painful diabetic peripheral neuropathy?
   a. Venlafaxine
   b. Milnacipram
   c. Tricyclic Antidepressants
   d. Duloxetine

Answer: d

9. Which of the following is true about the centrally acting muscle relaxants?
   a. There is an abundance of evidence on the efficacy to treat chronic pain
   b. Cyclobenzaprine is structurally related to the tricyclic antidepressants which may explain its effect on chronic pain
   c. They relax muscle through a direct effect on muscle fibers
   d. They have few side effects and generally well tolerated.

Answer: b
10. Which of the following statements about nonpharmacologic therapies are true?
   a. Massage is generally more effective as a single modality than when performed together with active exercises
   b. The evidence shows that acupuncture consistently results in a prolonged analgesia after treatment
   c. Cognitive behavioral therapy uses education linked with psychological therapies to help the patient control their pain.
   d. Nonpharmacologic therapies should only be considered in patients that fail pharmacological and interventional therapies

Answer: c
Biography

Dr. Wallace received a BS in biology from New Mexico State University in 1983. He then attended medical school at Creighton University School of Medicine in Omaha, Nebraska, where he received an M.D. in 1987. Dr. Wallace completed an internship in general surgery at the Washington Hospital Center in Washington, DC followed by an Anesthesiology residency at the University of Maryland. He remained on faculty at the University of Maryland Medical School in the Department of Anesthesiology before accepting a position as a training grant fellow in pain research at the University of California, San Diego. From 1992-1994, Dr. Wallace performed laboratory research in where he studied spinal drug delivery in a rat and dog model. During this time he also completed a Clinical Pain Fellowship in the Department of Anesthesiology. Dr. Wallace was on faculty at the University of Texas, Houston Medical School from 1994-1995 after which he returned to the University of California, San Diego and assumed the Directorship of the Center for Pain Medicine. He currently is the Chair, Division of Pain Medicine in the Department of Anesthesiology. Dr. Wallace is Associate Editor for the Clinical Journal of Pain, on numerous editorial boards, chair of the University of California San Diego IRB, and a nationally recognized lecturer on pain medicine. He has received numerous research grants from agencies including NIH, State and private foundations. Dr. Wallace has authored and co-authored more than 150 articles, abstracts, books, and book chapters concerning pain research and management. His research interests include human experimental pain, spinal drug delivery and the use of the cannabinoids in pain management. His hobbies include swimming and cruising the ocean waters of Southern California.
CLINICAL ASSESSMENT OF PAIN

Mark S. Wallace, M.D.
Professor of Clinical Anesthesiology
University of California San Diego
A. Dimensions of the Pain Experience

Pain is not only a sensory experience but also has unpleasant affective qualities which arouses and motivates the organism into activities directed at stopping the pain. Because pain is much more than a purely sensory experience, it has been suggested that there are three major psychological dimensions of pain: sensory-discriminative, motivational-affective, and cognitive-evaluative.

1) sensory-discriminative dimension - subserved by the rapidly conducting spinal systems. Provide perceptual information on location, magnitude and spatiotemporal properties of the pain.
2) motivational-affective - subserved by the reticular and limbic structures which are influenced by the slower conducting spinal systems. Provide motivational tendencies toward escape or attack.
3) cognitive-evaluative - subserved by the frontal cortex where personality traits are located. Reaction to pain is based on past experiences.

B. Assessing Pain Intensity

1) Verbal Rating Scales - consists of a list of adjectives describing the different levels of pain. Scores are usually assigned to each adjective for comparison between and within patients.

<table>
<thead>
<tr>
<th>TABLE 9.1. Verbal Rating Scales of Pain Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Point Scale</td>
</tr>
<tr>
<td>Scale</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>Mild</td>
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<tr>
<td>Moderate</td>
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<tr>
<td>Severe</td>
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<tr>
<td>Very severe</td>
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</tbody>
</table>
2) Visual Analogue Scale - consists of a 10 cm line with No Pain at one end and Worst Imaginable Pain at the other end. Patient is asked to place an X on the line that corresponds to intensity of pain. Score is assigned by measuring in millimeters the distance from the No Pain end to the X. Only measurement that can be treated as ratio data during statistical analysis.

3) Graphic Rating scales - same as visual analogue scale but has adjectives or numbers at specific points along the line.

4) Numerical Rating Scales - patient is asked to rate their pain from 0 to 10 (11 point scale) or 0 to 100 (101 point scale). 0 represents No Pain and 10 (or 100) represents Worst Imaginable Pain.

5) Behavior Rating Scales - based on the degree to which the pain interferes with concentration and daily activities. Scores are assigned to each level of interference.

**TABLE 9.2. Behavior Rating Scale of Pain Intensity**

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No pain</td>
</tr>
<tr>
<td>1</td>
<td>Low level pain that enters awareness only when I pay attention to it</td>
</tr>
<tr>
<td>2</td>
<td>Pain exists, but can be ignored at times</td>
</tr>
<tr>
<td>3</td>
<td>Pain exists, but I can continue performing all the tasks I normally would</td>
</tr>
<tr>
<td>4</td>
<td>Very severe pain that makes concentration difficult, but allows me to perform tasks of an undemanding nature</td>
</tr>
<tr>
<td>5</td>
<td>Intense, incapacitating pain.</td>
</tr>
</tbody>
</table>

6) Picture Scale - uses eight drawings of facial expressions of persons experiencing different levels of pain. Scores are assigned to each facial expression.

![Facial Expressions](image)


7) Box Scale - considered a combination of an 11-point numerical rating scale and the visual analog scale.

If a zero means “no pain” and a ten means “pain as bad as it could be,” on this scale of 0 to 10, what is your level of pain? Put an “X” through that number.

![Score Scale](image)

8) Descriptor Differential Scale - consists of a list of adjectives describing different levels of pain intensity. Patients are asked to rate the intensity of their pain as being more or less than each word. (Table 9.3)

C. Assessing Pain Affect

1) Verbal Rating Scale - same as verbal rating scale used to measure pain intensity, but, descriptors are those that describe discomfort or suffering.

<table>
<thead>
<tr>
<th>TABLE 9.5. Verbal Rating Scales of Pain Affect</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-Point Scale*</td>
</tr>
<tr>
<td>Bearable</td>
</tr>
<tr>
<td>Disturbing</td>
</tr>
<tr>
<td>Unpleasant</td>
</tr>
<tr>
<td>Uncomfortable</td>
</tr>
<tr>
<td>Distressing</td>
</tr>
<tr>
<td>Oppressive</td>
</tr>
<tr>
<td>Miserable</td>
</tr>
<tr>
<td>Awful</td>
</tr>
<tr>
<td>Frightful</td>
</tr>
<tr>
<td>Dreadful</td>
</tr>
<tr>
<td>Horrible</td>
</tr>
<tr>
<td>Agonizing</td>
</tr>
<tr>
<td>Unbearable</td>
</tr>
<tr>
<td>Intolerable</td>
</tr>
<tr>
<td>Excruciating</td>
</tr>
</tbody>
</table>

2) Visual Analogue Scale - same as visual analogue scale used to measure pain intensity, but, end-points describe discomfort or suffering.

3) Descriptor Differential Scale - same as descriptor differential scale used to measure pain intensity, but, descriptors are those that describe discomfort or suffering. (Table 9.6)

4) Pain Discomfort Scale - designed to assess negative affect that patients attribute to their pain and pain problems. Consists of ten items affirming (or denying) different affective responses to pain. (Table 9.7)

D. Assessing Pain Location
Instrument most commonly used is the pain drawing.

![Pain Drawing](image)

E. The McGill Pain Questionnaire (MPQ)
The MPQ combines all three measurements described above (intensity, affect, and location) into one form to describe the total pain experience. The MPQ consists of a list of words which describe the total pain experience. These words are categorized into three major classes and 16 subclasses. The three major classes are the three dimensions of the pain experience described above (sensory-discriminative, motivational affective, and cognitive-evaluative). There are ten subclasses under the sensory-discriminative class, five subclasses under the motivational-affective class, and one under the cognitive-evaluative class. The MPQ also asks the patient to locate their pain on a pain drawing and rate their pain on a scale of 0 to 5. (Figure 10.2)
Physiological Responses to Pain

Physiological measures of pain include heart rate, blood pressure, electrodermal activity, electromyography, and cortical-evoked potentials. These measures initially correlate well with pain intensity, however, over time they habituate in spite of persistence of the painful stimulus. These measures may also occur in the presence of non-painful states such as arousal and stress.

Assessing Pain in Children

1) Visual Analogue Scale - as described above for adults. Reliable for children over 5 years of age

No Pain ----------------------------------------------- Pain as bad

As it could be

Fig. 16.1 Visual analogue scale.

2) The Poker Chip Tool - child chooses one to four poker chips representing the "pieces of hurt". Reliable for children 4-5 years old.

3) Face Scales - consists of faces expressing varying amounts of distress. Reliable for children 6-8 years old.

Fig. 16.3 Faces scale. (From Bieri et al 1990 with permission)
4) The Oucher Scale - variant of the faces scale has six photographs of children in varying degrees of pain. Reliable for children 3-12 years of age.

5) Behavioral Measure of Pain - These measures rely on the observer to rate pain intensity based on behaviors expressed by the infant. These measures monitor cries and other vocalizations, facial expressions, or general body movements and are used to assess pain in infants.
   a) Infant Pain Behavior Rating Scale
   b) Postoperative Comfort Score
   c) Pain / Discomfort Scale
   d) Douleur Enfant Gustave-Roussy Scale
   e) Procedural Behavioral Rating Scale
   f) Procedure Behavior Checklist
   g) Observational Scale of Behavioral Distress
   h) Children's Hospital of Eastern Ontario Pain Scale
   i) Emergency Room Distress Behavior Checklist

6) Physiological Responses to Pain
   a) Heart rate - most widely used measure of pain in children and infants. In general, heart rate increases with increased pain, however, this response is less reliable in premature infants.
   b) Transcutaneous oxygen - reduced with pain
   c) Palmar sweating - increased with pain
   d) Blood pressure - poorly correlates with pain
H. Diagnosis of Neuropathic Pain

There is no one diagnostic test for the presence of neuropathic pain. No single symptom or sign is pathognomonic. The diagnosis should begin with a detailed description of the pain given by the patient. Neuropathic pain is described by a variety of terms such as burning, shooting, or lancinating and may be present without demonstrable physical findings. Several studies have evaluated the correlation between symptoms and the presence of NeP. Backonja et al demonstrated that NeP sensations are diverse, but three symptoms—numbness, tingling, and increased pain due to touch—appear to predominate. These symptoms illustrate the negative (sensory deficit) as well as positive (paresthesia and allodynia/hyperalgesia) phenomena that distinguish neuropathic from nociceptive pain. Rasmussen et al studied the symptoms and signs in patients with suspected neuropathic pain and found that brush-evoked pain was more frequent in NeP, high intensity of superficial ongoing pain and touch or cold provoked pain was associated with possible or definite NeP. The McGill Pain Questionnaire, and intensity of deep ongoing pain and paroxysms were similar in NeP and non NeP. A study by Bouhassira compared symptoms associated with NeP and somatic pain. They found that burning, electric shocks, tingling, pins and needles, itching, and numbness occurred more frequently in NeP. Bennett et al evaluated the ability of the Leeds Assessment of Neuropathic Symptoms and Signs pain scale (S-LANSS) to detect NeP. The S-LANSS is a 7 item questionnaire about the patient’s pain experience. A score of 12 or more suggests pain of predominantly neuropathic origin. The authors found that the S-LANSS is a valid and reliable self-report instrument for identifying neuropathic pain. Because NeP is highly heterogenous, it has been suggested that there are subgroups that may respond differently to pharmacologic intervention. The Neuropathic Pain Symptom Inventory is a specific self-questionnaire for the assessment of the different symptoms of neuropathic pain. The validation of this questionnaire suggests that it may be useful to detect differences in pharmacologic response to treatment.

A thorough neurologic examination is an essential part of the assessment of a patient with chronic pain and helps confirm the diagnosis of a neuropathic pain disorder. Allodynia is assessed to determine if the injury responds to static, dynamic, or thermal pressure. These assessments can be conducted through a light rub with a fingertip, cotton swab, or paintbrush (dynamic allodynia); by applying perpendicular pressure slowly with a cotton swab or pencil eraser (static allodynia); and with a warm or cold test tube or tuning fork (thermal allodynia).

Hyperalgesia is diagnosed if the patient has an exaggerated response to single or multiple pinpricks. Summation (increasing pain to each repeated stimulus although each stimulus is the same) and after-sensation (exceptionally long perception of a stimulus after it has been administered) usually occur during neuropathic pain. The examination of motor elements is to detect both negative and positive signs. Negative signs include weakened muscles, lowered endurance, and hypotonia. Positive signs are increased muscle tone, tremor, dystonia, and dyskinesia. Patients also should be examined for coordination, ataxia, and apraxia. An examination of the motor system provides an important indication that the nervous system, not only the pain-transmitting fiber, is injured. An examination of the autonomic nervous system should seek to determine if the area of pain has abnormally hot or cold skin temperature changes, if the skin color has changed, if abnormal sweating has occurred or if the skin is unusually dry, or if abnormal hair and nail growth is present. Although all of these examinations are important, it should be emphasized that all successful diagnosis and treatment begins with the physician acknowledging the reality of the patient’s pain.
In general, there is no single diagnostic test for neuropathic pain. Diagnostic studies can help confirm diagnostic impressions or rule out underlying causes (eg, rheumatologic causes) and diagnostic imperatives (eg, metastases in the cancer patient with new back pain). Blood studies can help identify systemic illnesses (eg, acute herpes virus infection) associated with neuropathies. Magnetic resonance imaging (MRI) can identify structural lesions, such as tumors or infections in the spine or plexus.

Computed tomography (CT) is similar to MRI, except it is less sensitive to soft tissue lesions. Electromyography (EMG) and nerve conduction velocity (NCV) testing can help localize a neuropathy (eg, Is it a root or plexus neuropathy?), grade its severity, and help categorize the pathophysiology (axonal vs demyelinating). Quantitative sensory testing (QST) assesses small-fiber function, and can show abnormalities consistent with neuropathic pain even when an EMG and NCV are normal. These studies have important limitations. First, they do not measure pain and a patient may have neuropathic pain and normal studies, or have abnormal studies with no pain. Second, an EMG and NCV assess only large nerve fibers, which have little involvement in pain.

I. Experimental Pain Models in Human Subjects

1) Mechanical Pain
   a) Pinch algometer - device consists of a pistol shaped handle and a shaft with 2 circular probes facing each other (area= 1 cm²). One probe is stationary while the other is moveable. A fold of skin is placed between the 2 probes and 1 is displaced slowly and evenly (rate 30 kPa/sec) towards the other, pinching the skin. A transducer in 1 of the probes provides constant feedback (via a digital computer) of the pressure exerted against the probe. The subject is instructed to press a switch at the very instant of pain experience; the trial is terminated. Pain thresholds are defined as the mean pressure for three trials. Stimuli are given at 1 minute intervals.
   b) Pressure algometer - similar to pinch algometer but pressure is applied instead of pinch.

2) Thermal Pain
   a) Hot pain - an electrode applied to the skin is heated at a rate of 1.5°C/second (starting at a baseline of 32°C). When the subject perceives pain, a button is pushed which returns the electrode temperature to baseline. Normal hot pain threshold is between 42-44°C.
   b) Cold pain - an electrode applied to the skin is cooled at a rate of 1.5°C/second (starting at a baseline of 32°C). When the subject perceives pain, a button is pushed which returns the electrode temperature to baseline. Normal cold pain threshold is between 10-12°C.

3) Experimental Central Facilitation
   a) Intradermal capsaicin - capsaicin is a derivative of red chili pepper and when applied to mucous membranes or injected into the skin will cause an intense burning pain lasting 1-3 minutes. This is followed by an area of hyperalgesia around the injection site which results from dorsal horn cells becoming hypersensitive to incoming stimuli. Thus the subject will report a normally non-painful stimulus as painful. This technique is performed by injecting 10 mcl (100mcg) of capsaicin intradermally. The investigator records the magnitude of the pain at 5 minute intervals. At 20 minutes, the edge of the
region of hypersensitivity is established by dragging a cotton wisp toward the injection site until pain is reported. By doing this concentrically, the hypersensitive area is mapped out. This mapping is repeated with the application of a von Frey filament concentrically and a small electrode heated to 38°C. The capsaicin will result in a small area of hypersensitivity to heat, a larger area of hypersensitivity to a cotton wisp and yet a larger area of hypersensitivity to the von Frey filaments.

b) Train of 4 electrical stimulation - Electrical shocks delivered by means of a cutaneous electrical nerve stimulator evokes a distinct perception of first and second pain. The trains of 4 are delivered at a frequency of 1 shock/1.6 seconds and the subjects are asked to rate the first and second pain on a visual analogue scale.

c) Train of 3 heat pulses - Heat pulses delivered with a peak intensity of 52°C (from a baseline of 40°C at 10°C/sec). Trains of 3 pulses are delivered at a frequency of 1 pulse/2.8 seconds and the subjects are asked to rate the first and second pain on a visual analogue scale.
TABLE 9.6. Descriptor Differential Scale of Pain Affect

*Instructions:* Each word represents an amount of sensation. Rate your sensation in relation to each word with a check mark.

- Slightly unpleasant
- Slightly annoying
- Unpleasant
- Annoying
- Slightly Distressing
- Very Unpleasant
- Distressing
- Very annoying
- Slightly intolerable
- Very distressing
- Intolerable
- Very intolerable


---

TABLE 9.3. Descriptor Differential Scale of Pain Intensity

*Instructions:* Each word represents an amount of sensation. Rate your sensation in relation to each word with a check mark.

- Faint
- Moderate
- Barely strong
- Intense
- Weak
- Strong
- Very mild
- Extremely intense
- Very weak
- Slightly intense
- Very intense
- Mild

### TABLE 9.7. The Pain Discomfort Scale

**Instructions:** Please indicate by circling the appropriate number whether each of the statements below is more true or false for you. Please answer every question and circle only one number per question. Answer by circling the appropriate number (0 through 4) according to the following scale:

- **0 =** This is very untrue for me.
- **1 =** This is somewhat untrue for me.
- **2 =** This is neither true nor untrue for me (or it does not apply to me).
- **3 =** This is somewhat true for me.
- **4 =** This is very true for me.

<table>
<thead>
<tr>
<th>Statement</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I am scared about the pain I feel.</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. The pain I experience is unbearable.</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. The pain I feel is torturing me.</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. My pain does not stop me from enjoying life.*</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. I have learned to tolerate the pain I feel.</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6. I feel helpless about my pain.</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. My pain is a minor annoyance to me.*</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8. When I feel pain I am hurting, but I am not distressed.*</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>9. I never let the pain in my body affect my outlook on life.*</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>10. When I am in pain, I become almost a different person.</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>


*These items are reverse scored.
REFERENCES


FIGURE 10.2. McGill Pain Questionnaire. The descriptors fall into four major groups: sensory, 1 to 10; affective, 11-15; evaluative, 16; and miscellaneous, 17-20. The rank value for each descriptor is based on its position in the word set. The sum of the rank values is the pain rating index (PRI). The present pain intensity (PPI) is based on a scale of 0 to 5. Copyright 1975 Ronald Melzack.
PHARMACOLOGY

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Opioid Pharmacology

Drugs used in pain therapy are divided into analgesics and co-analgesics. The analgesic drugs are those that have intrinsic analgesic properties and include the opioids, nonsteroidal anti-inflammatory drugs and acetaminophen. The co-analgesics are drugs used in pain management which may or may not have intrinsic analgesic properties but may provide pain relief in certain pain syndromes or potentiate the common analgesics. This chapter will discuss the pharmacology of the opioids and give guidelines for prescribing.

The opiates come from the seed capsule of the opium poppy (Papaver somniferum). Opioids, which means opiate-like, are derivatives of opium and include naturally occurring opium derivatives, partially synthetic derivatives of morphine, and synthetic compounds. (Table 3.1) The term narcotic means any drug that produces narcosis and therefore is a misnomer to opioids. The term narcotic is used by the drug enforcement agency to include drugs other than the opioids, such as cocaine; therefore, opioid is a more specific term.

The opioids are the most powerful pain reliever known to man. Unfortunately, there are many misconceptions about opioid use which hinder proper prescribing by the physician. Historically, in the 60’s and 70’s opioids were rarely used because of fears of drug addiction, diversion and abuse. In the 90’s, reports started surfacing on the underutilization of the opioids for the treatment of pain, and practitioners were encouraged to use them more liberally. This resulted in a surge in use of the opioids. Probably due to poor patient selection, there has also been a surge in misuse and diversion. Now the pendulum is swinging back toward the middle. We are now in an era of moderation and balance with an emphasis on safety. The opioids continue to be an important therapy for chronic pain; however, the patients must be properly selected and monitored in order to maximize efficacy and reduce risks.

Opioid Pharmacodynamics

Opioid Receptors - Pharmacodynamics is defined as the effect of the drug on the body and is the study of the drug effect at the receptor level. There are five groups of opiate receptors which are widely located in the body. (Table 3.2) They are present in the brain, spinal cord, peripheral nerves and ganglia, adrenal medulla, and gut. The different receptors produce different pharmacologic actions depending on their location. Most of the receptors in the brain are located in the periaqueductal grey. Stimulation of these receptors activate descending fibers which modulate C-fiber input into lamina II of the spinal cord. The modulating neurotransmitters released in the spinal cord are norepinephrine and serotonin. Spinal cord opiate receptors are located in lamina II (substantia gelatinosa). When stimulated, opioid receptors inhibit the release of substance P from the presynaptic terminal and increase potassium conductance in the postsynaptic terminal. Controversy exists on the role of peripheral receptors in analgesia,
however, stimulation of the receptors on nerve terminals results in inhibition of substance P release.

**Side Effects** - The most common side effects seen with opioid therapy are respiratory depression, nausea and vomiting, constipation, and pruritis. Fortunately, the blood level of the opioid required to cause side effects is usually much higher than that required for analgesia. Also, these side effects are usually easily treated. Respiratory depression is the most serious side effect but is rarely seen with the most common doses used in daily practice. It is produced by stimulation of the opiate receptors located in the brainstem. It is more likely to occur in opioid naive patients and in very high doses. Also, pain stimulates respirations which counteract the respiratory depression seen with the opioid. Respiratory depression is rarely seen if opiates are titrated slowly to achieve the analgesia.

Nausea and vomiting (N/V) is a less serious side effect of the opioids but can be a great hindrance to effective use of the drug. In order to properly treat N/V, the physician must have an understanding of the physiology of N/V. The vomiting center is located in the brainstem and activated by three areas: the chemoreceptor trigger zone (CRTZ), the vestibular system (VS), and the gastrointestinal tract (GI). The CRTZ is directly activated by the opioids. It is also activated by dopamine and serotonin; therefore, the antidopaminergics (i.e. prochlorperazine) and the antiserotonergics (i.e. odansetron) prevent activation. The opioids sensitize the vestibular apparatus to movement which can result in N/V. The VS is also sensitized by the cholinergics and histamine, therefore the anticholinergics (i.e. scopolamine) and the antihistaminergics (i.e. diphenhydramine) prevent sensitization. Therefore, patients who complain of dizziness and N/V with movement would most likely benefit from drugs that prevent VS sensitization. Opiates also decrease GI motility which may exacerbate N/V. Metoclopramide is a good treatment for opioid induced N/V because of its antidopaminergic activity as well as increasing GI motility. (Figure 3.1)

Constipation and pruritus are minor side effects of the opioids and are usually easily managed. Constipation results from the activation of the mu receptor in the GI tract. Prophylactic bowel maintenance is the most effective way to manage opioid induced constipation but mild laxatives may also be used. For severe cases, Methyl-naltrexone is approved for use in cancer or palliative care and may be administered subcutaneously to treat opioid-induced constipation.

Pruritus results from activation of the mu receptor in the spinal cord. It is more commonly seen with the intraspinal administration of opioids which will be discussed later. A summary of the management of opioid induced side effects are found in Table 3.3.

**Tolerance and Dependence** - Tolerance is defined as a decreased effect of a drug following repeated administration or increasingly greater doses required to achieve the desired effect. Both the physician and patient must understand this phenomenon to avoid escalating the dose of the opioid to unacceptable levels in an attempt to maintain pain relief. It is common to develop tolerance to the supraspinal effects of the opioids such as
analgesia, respiratory depression, euphoria, dysphoria, sedation, and N/V. Tolerance does not occur with constipation and miosis. It is more likely to develop tolerance with rapidly increasing doses or large doses with short dosing intervals and usually occurs after about 2-3 weeks of continuous administration. Tolerance can be reversed after a 2-3 week drug-free interval. This procedure is called a drug holiday and is accomplished by slowly tapering the opioid over 10-14 days and maintaining a drug-free interval of 2-3 weeks. The opioid can then be restarted at a lower dose with better pain relief achieved. It is very common for chronic pain patients to maintain a stable opioid dose for years without developing tolerance. However, if the dose escalation becomes a problem, a drug holiday should be considered.

Dependence is divided into physical dependence and psychological dependence. Physical dependence is a pharmacologic property of all opioids and means that withdrawal symptoms will occur if the opioid is abruptly discontinued or if an antagonist is administered. Withdrawal occurs because the exogenous administration of opioids suppresses the normal endogenous production of opioids. If the exogenous source is abruptly stopped, the body lacks the normal blood levels of endogenous opiates and withdrawal will occur. Table 3.4 summarizes the signs and symptoms of opioid withdrawal. Withdrawal can be prevented with a slow taper over 10-14 days in order to allow the body to restart the endogenous opioid production. Unlike benzodiazepine and barbiturate withdrawal, opioid withdrawal is not life threatening to the patient. The physician must keep this in mind when managing the noncompliant patient. If the patient is self-medicating, it is acceptable to abruptly withhold the opioid. This, of course, is only after making attempts to taper the opioid slowly. These patients would best be managed in a detoxification program. (See chapter on the difficult pain patient) Psychological dependence is commonly referred to as addiction. It is defined as a psychological and behavioral syndrome characterized by compulsive drug use, overwhelming interest in securing a supply, and return to drug use after drug detoxification. Addicted persons may exhibit drug hoarding, acquisition of drugs from multiple sources, increasing drug dosage on their own, and drug sales. Unfortunately, chronic pain patients on chronic opioid therapy are all too often labeled as addicts. There is considerable evidence that addiction is a rare outcome of opioid use by patients, at least among those with no prior history of drug abuse. Causes of addiction lie more in the psychology of the patient and in the environment than in the qualities of the medically administered drugs. The chapter on the difficult pain patient will address these issues in more detail.

Opioid Pharmacokinetics

An understanding of opioid pharmacokinetics is essential to proper prescribing of this class of analgesics. Pharmacokinetics is defined as the effect of the body on the drug and will influence how the drug is administered. This section will briefly discuss the pharmacokinetics of the opioids in hopes of giving a better understanding of prescribing practices.

Absorption - Most of the opioids administered in outpatients is via the oral route. All opioids are readily absorbed in the GI tract but due to the first pass effect through the liver, the bioavailability of the various opioids will differ. An example is methadone which has a very low hepatic clearance and therefore the intravenous dose is just slightly lower than the oral dose. Morphine has a high hepatic clearance therefore the oral dose is three times the intravenous dose. These principles become important when trying to convert from an
intravenous opioid regimen to an oral regimen. Table 3.5 gives the equianalgesic dose and parenteral-to-oral dose ratio for the most commonly used opioids. It is possible to administer opioids rectally which bypasses the first pass effect but results in erratic absorption.

A new method of delivering opioids is transdermally. Drugs delivered by this route must have a high lipid solubility, high potency, and low molecular weight. The only opioid available for this route is fentanyl which meets all of the requirements. The fentanyl patch is a system which is composed of four functional layers: 1) an occlusive backing which prevents loss of drug and entry of water into the drug system; 2) a drug reservoir mixed with alcohol which increases the permeability of the skin to fentanyl and enhances the rate of drug flow; 3) release membrane adhesive which controls the rate of drug release from the reservoir (a fentanyl saturated silicone layer holds the system in place and effectively administers a bolus of fentanyl after application; 4) protective peel strip. The penetration of the fentanyl through the skin varies from 46-66% and variations in drug penetration between skin regions can vary 20-40%. The onset of analgesia does not occur for about two hours due to the formation of a skin depot. Once the skin becomes saturated, the fentanyl is absorbed into the vasculature. Because of this skin depot, appreciable plasma levels last 8-12 hours after removal of the patch. Factors which increase fentanyl absorption include vigorous exercise, excessive hydration, occlusion of the skin surface, skin damage, hyperfunction of the sweat glands, and hyperthermia.

**Distribution/Metabolism/Elimination** - The volume of distribution of a drug is the apparent volume a drug must be distributed if the concentration everywhere is equal to that in the plasma. This volume is dependent upon the lipid solubility, protein binding and ionization of the drug. Because of differences in lipid solubility, protein binding and ionization, all of the commonly used opioids have similar volumes of distribution and therefore will not be discussed further.

All of the opioids are hepatically metabolized. Opioids metabolism depends more on plasma concentration and hepatic blood flow than on the intrinsic microsomal activity, therefore, liver dysfunction has little effect on opioid metabolism unless it is severe. Therefore, it is rarely required to decrease the dose in liver dysfunction. All of the opioids are metabolized into inactive metabolites except morphine and meperidine. Morphine-6-glucuronide, a metabolite of morphine, is 200X more potent as an analgesic than morphine but because of the poor penetration of the blood brain barrier, this analgesia is not appreciated. Meperidine is metabolized to normeperidine which has half the potency of meperidine. However, normeperidine may induce seizures if plasma levels are high enough.

The kidneys excrete the metabolites of the opiates, therefore, in renal disease the metabolites may accumulate. This problem becomes significant in the use of meperidine because of the metabolite normeperidine as discussed above. Because of this, the maximum recommended daily dose is 800 mg. Also, morphine-6-glucuronide may serve as a reservoir of morphine since morphine may be released from morphine-6-glucuronide via plasma hydrolysis and made available to cross the blood-brain barrier.
Opioid Monograms

There are many opioids available for the management of acute and chronic pain. Some opioids have very different pharmacologic properties which affects the administration. They also come in different preparations which will effect administration. We will describe the most commonly used opioids. Opioids are divided into agonists, agonist-antagonists, and antagonists. The agonists bind to one or more of the opiate receptors and activate them. The agonist-antagonists have agonist activity on one receptor with antagonist activity at another. The antagonists bind to the receptors without activation therefore they block agonist activity. The antagonists as well as the agonist-antagonists may induce withdrawal symptoms in opioid dependent patients because of mu antagonism. Antagonists are frequently used to reverse life-threatening side effects of opioids such as respiratory depression from opioid overdose. They are rarely used on a chronic basis. Table 3.6 lists the opioids.

**Morphine.** Morphine sulfate is the reference standard for all opioids. Its oral bioavailability is approximately one-third the intravenous dose therefore when converting from intravenous to oral morphine, the dose must be tripled. It comes in an immediate release preparation and a controlled release preparation. The immediate release preparation has an onset of 15-20 minutes and duration of 3-4 hours. The controlled release preparation has a slow onset but a prolonged duration of 8-12 hours. Controlled release morphine is embedded in a wax base which slowly releases the morphine. The analgesia peaks in 90-120 minutes (compared to 30-90 minutes for the immediate release). The tablet cannot be broken as this will release a large quantity of the morphine. Immediate release morphine should be given every 3-4 hours and controlled release morphine every 8-12 hours (oramorph, mscontin) or every 12-24 hours (kadian, avinza). Oramorph, mscontin and kadian do not have an immediate release component of the drug and peak plasma levels occur about 2 hours after dosing. Avinza has an immediate release component resulting in early peak plasma levels. Kadian comes in a capsule that can be opened and sprinkled in food and still retains the controlled release effect. It is common to administer controlled release morphine on a time contingent basis (every 8-12 hours) and immediate release morphine on an as needed basis for breakthrough pain (every 3-4 hours prn). This method allows for more stable blood levels of morphine without peaks and valleys commonly seen with as needed dosing. Morphine is also available in an elixir which is more readily absorbed than tablets.

**Methadone.** Methadone is slightly more potent than morphine. It is less dependence producing than morphine because there is less euphoria and less sedation with methadone. It has an oral bioavailability of almost 90% therefore the intravenous and oral dose are almost equivalent. Methadone is poorly metabolized by the liver therefore it has an extremely long half life. This makes the drug valuable in the prevention of withdrawal in drug addicts because it only requires once per day dosing. However, the analgesia half-life is much shorter therefore it is common to give methadone every 6-12 hours for pain control. This dosing schedule makes it very popular for chronic narcotic therapy. Methadone is also available in an elixir which is more readily absorbed than tablets. There has been a surge in reports of deaths related to methadone. Methadone is
used in less than 10% of subjects for pain control but accounts for over 30% of deaths related to opioid overdose. The pharmacokinetics of methadone make it difficult to titrate and now it is recommended that the opioid conversion table should not be used when initiating methadone and that it should be started at low doses and titrated slowly. There are also many drug interactions that can affect methadone metabolism. The drug has also been associated with prolonged Q-T interval and arrhythmia although the exact dose at which this occurs is not known and likely at high doses (>100mg/day).

**Meperidine.** Meperidine is less potent than morphine. It has a faster onset than morphine; therefore, the patient may experience more euphoria. Because of the metabolite normeperidine and the potential for seizures, it is not the opioid of choice. This effect of normeperidine may be significant at doses greater than 1 gram/day or in renal failure. In addition to analgesic effects, meperidine also has atropine-like effects and local anesthetic effects. The atropine-like effects may lead to tachycardia. Neuropathic pain syndromes that are resistant to opioids may respond to meperidine perhaps due to the local anesthetic action it possesses. Also, meperidine has been known to induce a syndrome characterized by tachycardia, increased blood pressure, arrhythmias and hyperthermia and even death in patients taking MAO inhibitors.

**Hydromorphone.** This opioid is 6-8 times more potent than morphine. It is easily absorbed from the GI tract and has less side effects than morphine. It has a fast onset and a short half life; therefore, it requires frequent dosing (every 2-3 hours). It is more commonly used on an as needed basis (to treat breakthrough pain) rather than a time contingent basis.

**Codeine.** Codeine is a weak opioid with less intense side effects. It has a higher oral bioavailability than morphine and a quicker onset, however, the duration is short. It is commonly given with Tylenol therefore it is not usually administered chronically because of the risk of Tylenol toxicity (see Tylenol toxicity, Chapter 6). Codeine is frequently used as an antitussive. Codeine is the methylated form of morphine and is metabolized to morphine. There is evidence that some patients lack the enzyme to convert codeine and are insensitive to codeine. This seems to occur more often in African Americans; however, this concept is controversial.

**Hydrocodone.** Hydrocodone has pharmacologic activity similar to codeine. It was previously used as an antitussive only but now is a commonly used analgesic. It is only available in a Tylenol preparation; therefore, the total daily dose is limited.

**Oxycodone.** Oxycodone is qualitatively similar to morphine in all respects. It is available in three preparations, oxycodone alone, oxycodone with Tylenol, and oxycodone with aspirin. It is also available in a time release preparation (oxycontin). Oxycontin has an immediate release component that results in early peak plasma levels. Purdue elected to reformulate OxyContin in 2010 in an effort to make the tablet more difficult to manipulate for the purpose of intentional misuse and abuse. The reformulated OxyContin is harder to crush and forms a gel when dissolved in liquid, making it harder to inject or inhale.
**Oxymorphone.** This opioid is 7-10 times more potent than morphine. It is a derivative of hydromorphone and comes in a 5 mg rectal suppository. It is also available in an immediate release and timed release preparation (Opana).

**Levorphanol.** Levorphanol is 4 times more potent than morphine. The incidence of nausea and vomiting, and constipation is less than with other agents. The duration is somewhat longer than morphine. This drug is no longer available on the market.

**Propoxyphene.** Propoxyphene is a derivative of methadone. It is less effective of an analgesic than codeine. Sixty mg is no more effective than 600 mg of aspirin and 32 mg is no more effective than placebo. It has an alleged lower dependence potential but this is disputed. The oral bioavailability is 50% and it has a large volume of distribution which accounts for its long half life of approximately 10 hours, however, its analgesic action is short.

**Fentanyl.** Fentanyl is 100 times more potent than morphine. It is available in a transdermal patch (See above under pharmacokinetics) for chronic constant pain as well as buccal formulations which are immediate release and result in fast onsets. Buccal fentanyl comes as a lozenge on a handle (Actiq), a tablet (Fentora), and a buccal soluble film (Onsolis) to dissolve in the mouth.

**New Formulations to reduce misuse.**

**Embeda.** Embeda is an extended-release oral morphine sulfate surrounding naltrexone inner core. It is bioequivalent to extended-release oral morphine formulations MSContin, oramorph, and generic extended-release morphine. August 2009, the FDA approved Embeda for the treatment of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. Embeda is the first FDA-approved long-acting opioid that is designed to reduce drug liking and euphoria when tampered with by crushing or chewing. The inner naltrexone core is encapsulated in a protective core preventing it’s absorption and interference with opioid binding. If tampered with by crushing or dissolving, the naltrexone core is released to interfere with morphine binding to opioid receptors in the body, potentially precipitating withdrawal in opioid-dependent individuals. Symptoms of withdrawal usually appear within 5 minutes and can last for up to 48 hours. The price of Embeda is higher however: Embeda 20mg BID - $276/month; Kadian 20mg BID –$285/month; MSContin 20 mg BID - $128/month; generic extended-release morphine sulfate 15 mg BID - $48.99/month.

**Partial Agonists**

**Buprenorphine.** Buprenorphine is a partial agonist that avidly binds to the opioid receptor resulting in a long half life. It is marketed for the treatment of drug dependence (suboxone). When administered after the patient starts experiencing withdrawal symptoms, buprenorphine will reverse withdrawal very effectively. However, if given together with a full agonist, it can displace the opioid from the receptor and induce withdrawal symptoms. It is generally used for office based detoxification. However, preparations are in development for the treatment of chronic pain.
**Agonists-antagonists**

**Butorphanol.** Butorphanol is a kappa and sigma agonist with weak mu antagonism. Because of the kappa agonism, significant sedation may result. There is 50% less nausea/vomiting than morphine and other side effects are less common. There may also be a dysphoria seen with this opioid. It is available in a nasal spray preparation. The success of this drug as a chronic analgesic has been limited and is not the opioid of choice.

**Pentazocine.** Pentazocine is a kappa and sigma agonist and mu antagonist. High doses may cause an increase in heart rate and blood pressure. There is a high incidence of psychomimetic effects (anxiety, dysphoria, nightmares, and hallucinations) which greatly limits the use of this drug. It is not the opioid of choice for chronic use.

**Antagonist**

**Naloxone.** Naloxone is a potent mu antagonist which is short acting (30-45 minutes). The short duration of this drug must be considered because the side effects treated may reoccur. It is available in an intravenous form only (0.4mg/cc) although an oral preparation will soon be available. The proper method of administration is to dilute the drug in 10 ml saline and titrate 1 ml every 1-2 minutes until the desired effect is reached. Bolus dosing of naloxone has been associated with tachycardia, hypertension, pulmonary edema and cardiac dysrhythmia which is thought to be the result of a sudden increase in sympathetic nervous system activity.

**Assessment of patients for opioid use**

Prior to initiating opioid, a thorough assessment of the patient is required to identify risks/benefits of therapy. Medical History Findings Associated With Substance Use Disorders include.

- **Medical history:** hepatitis C, HIV, TB, cellulitis, sexually transmitted diseases, elevated liver function tests, etc
- **Social history:** motor vehicle or fire-related accidents, DUlS, domestic violence, criminal history
- **Psychiatric history:** personal history of psychiatric diagnosis, outpatient and/or inpatient treatment, current psychiatric medications

Patient Care Agreements are recommended before starting opioid therapy. Essential components of such agreements include:

- Widely used but not evidence based
- Reminder: opioids → one modality in multifaceted approach to achieving goals of therapy
- Detailed outline of procedures and expectations between patient and doctor
- Prohibited behaviors, and grounds for tapering or discontinuation
● Limitations on prescriptions
● Emergency issues
● Refill and dose-adjustment procedures
● Exit strategy
● May contain elements of Informed Consent discussion
● Inclusion of above points will satisfy medico-legal issues

An example of an exit strategy may include:

● Criteria for tapering emphasized in the initial patient agreement
  − documentation of lack of pain reduction and/or lack of functional improvement
  − documentation of opioid medication or prescription misuse or abuse
  − positive urine screen test for any illegal substance
  − failure to comply with all aspects of treatment program

● Distinguish between abandoning opioid therapy, abandoning pain management, and abandoning patient

● Taper off opioid therapy, with or without specialty assistance

Identify high risk versus high worry patients
**High Risk = Risk of Adverse Medical Effects**

● COPD
● Dementia
● BPH
● Unstable gait
● Hazardous environment
● Pre-treatment constipation
● Hepatic insufficiency
● Low blood pressure
● Sleep apnea
● Methadone deaths

**High Worry = Risk of Abuse Behaviors**

● History of drug or alcohol abuse
• History of sexual, physical, or emotional abuse; especially early sexual trauma
• Criminal history
• Unclear cause of pain
• History of multiple pain clinicians
• Multiple tattoos
• Unstable home environment
• Too ingratiating; too demanding
• “Gut feeling”

Look for aberrant drug taking behaviors

Major
• Selling prescription drugs
• Prescription forgery
• Stealing or borrowing another patient’s drugs
• Injecting oral formulation
• Obtaining prescription drugs from nonmedical sources
• Concurrent abuse of related illicit drugs
• Multiple unsanctioned dose escalations
• Recurrent prescription losses

Minor
• Aggressive complaining about need for higher doses
• Drug hoarding during periods of reduced symptoms
• Requesting specific drugs
• Acquisition of similar drugs from other medical sources
• Unsanctioned dose escalation 1–2 times
• Unapproved use of the drug to treat another symptom
• Reporting psychic effects not intended by the clinician

Screening tools to assess risk of aberrant behavior with opioid use

• **Drug Abuse Screening Test – DAST**
  — 20-item questionnaire
• **Opioid Risk Tool – ORT**
Mark each box that applies:  

<table>
<thead>
<tr>
<th></th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Family history of substance abuse</strong></td>
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<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Illegal drugs</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Prescription drugs</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td><strong>Personal history of substance abuse</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Illegal drugs</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Prescription drugs</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td><strong>Age (mark box if between 16-45 years)</strong></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>History of preadolescent sexual abuse</strong></td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td><strong>Psychological disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADO, OCD, bipolar, schizophrenia</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Depression</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

**Scoring totals:**

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3</td>
<td>Low risk (6%)</td>
</tr>
<tr>
<td>4-7</td>
<td>Moderate risk (28%)</td>
</tr>
<tr>
<td>&gt;8</td>
<td>High risk (&gt;90%)</td>
</tr>
</tbody>
</table>
Screener and Opioid Assessment for Patients with Pain – SOAPP

Name: __________________________ Date: ________________

The following are some questions given to all patients at the Pain Management Center who are on or being considered for opioids for their pain. Please answer each question as honestly as possible. This information is for our records and will remain confidential. Your answers alone will not determine your treatment. Thank you.

Please answer the questions below using the following scale:

0 = Never, 1 = Seldom, 2 = Sometimes, 3 = Often, 4 = Very Often

1. How often do you have mood swings?
2. How often do you smoke a cigarette within an hour after you wake up?
3. How often have you taken medication other than the way that it was prescribed?
4. How often have you used illegal drugs (for example, marijuana, cocaine, etc.) in the past five years?
5. How often, in your lifetime, have you had legal problems or been arrested?

Please include any additional information you wish about the above answers. Thank you.

Guidelines for Prescribing Opioids for Chronic Pain

Because of the many problems with opioids, such as side effects, tolerance, dependence, potential misuse, and legal issues, the chronic administration of opioids must be done with caution. However, unfortunately many patients are denied the potential benefits of opioids because of misconceptions. In general, terminally ill patients experiencing pain should never be denied opioids if it is determined they will benefit. The treatment of chronic benign pain with opioids is somewhat controversial. Many chronic benign patients can in fact benefit from long term opioid therapy. Table 3.7 gives general guidelines for chronic opioid therapy in chronic benign pain.

In summary, the following guidelines should be followed:
1. Watch for and treat all side effects
2. Be cautious in starting chronic opioid therapy in:
   a. Young patients
   b. Severe psychological pathology (personality disorders, schizophrenia, depression; chaotic family or social environment.
c. Prior history of chemical dependency
d. Strong family history of drug abuse
c. Questionable pain diagnosis (pain with the lack of objective findings such as imaging, disease process)

3. Patients with a low risk of abuse potential are middle age to older patients with no prior history of drug or alcohol abuse with a stable family/social environment.

**Intravenous and Subcutaneous Opioid Therapy**

It is not uncommon for end stage cancer patients to require the intravenous administration of opioids. This can be accomplished with an intravenous patient controlled analgesia pump (IVPCA) which can easily be managed in the comfort of the patient's home. The decision to change from oral opioids to intravenous opioids depends on many factors but in general, if the patient is requiring large doses of opioids with frequent episodes of breakthrough pain, an IVPCA may be beneficial. It is easier to titrate the opioid to effect with the IVPCA than with oral opioids. However, IVPCA therapy requires intravenous access. This can be accomplished with a central line or a peripheral line with a subcutaneous port and most home health care nurses can easily access these systems. Table 3.8 gives guidelines for IVPCA therapy with an example.

It is also possible to administer opioids via a PCA subcutaneously (SQPCA). This has the advantage of not requiring intravenous access. However, the disadvantages include less predictable blood levels than with IV opioids and also minimal pain on injection. Injection pain is minimized by concentrating the opioid in order to decrease the volume of the injectate required. The injection site should be moved to different parts of the body periodically to avoid cellulitis. As with IVPCA, this technique can easily be managed by a home health care nurse. The same guidelines that apply to the IVPCA apply to SQPCA except the opioid should be in concentrated form (i.e. morphine 10 mg/cc).

**Intraspinal Opioid Therapy**

Intraspinal opioid therapy is a technique used by pain specialists to provide potent analgesia. Pain impulses travel to the central nervous system via the slow conducting A-delta and C fibers. The C fibers synapse on neurons in lamina II of the spinal cord. This lamina is called the substantia gelatinosa and is rich in opioid receptors. This is the site of intraspinal opioid action. By delivering the opioid into the epidural space or the intrathecal space, much smaller doses are required, therefore, systemic side effects are less likely. However, since many of the systemic side effects of opioids are mediated through the spinal cord and brainstem receptors, these side effects may still occur with intraspinal opioids. Intraspinal opioid therapy is commonly used for postoperative pain management. This is usually accomplished by infusing the opioid into the epidural space.

Whereas acute intraspinal opioid infusions are accomplished by the epidural administration of the opioid, chronic administration requires the drug to be delivered intrathecally. This is because much smaller volumes are required for intrathecal
administration. Chronic delivery of intraspinal opioid is accomplished with an implantable pump that has a drug reservoir which is accessed percutaneously. This drug reservoir is approximately 20 cc and the infusion rates are approximately 0.1-0.5 cc per day. Thus the pump will only require refilling every 1-2 months. These pumps are very expensive to place, therefore, are not recommended for patients with a short life expectancy. An alternative and much more cost effective technique, in these patients is the placement of an epidural catheter with a percutaneous access port. This port can be accessed and connected to an external patient controlled analgesia pump. With this technique, the patient can self-administer the intraspinal opioids for pain relief.

**Suggested Reading**


<table>
<thead>
<tr>
<th>Naturally occurring opium derivatives</th>
<th>Partially synthetic derivatives of morphine</th>
<th>Synthetic compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Heroin</td>
<td>Alfentanil</td>
</tr>
<tr>
<td>Codeine</td>
<td>Hydromorphone</td>
<td>Fentanyl</td>
</tr>
<tr>
<td></td>
<td>Oxycodone</td>
<td>Levorphanol</td>
</tr>
<tr>
<td></td>
<td>Oxymorphone</td>
<td>Meperidine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Methadone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Propoxyphene</td>
</tr>
<tr>
<td>Opioid receptors and actions</td>
<td>MU</td>
<td>KAPPA</td>
</tr>
<tr>
<td>------------------------------</td>
<td>----</td>
<td>--------</td>
</tr>
<tr>
<td>Analgesia</td>
<td></td>
<td>Analgesia</td>
</tr>
<tr>
<td>Euphoria</td>
<td></td>
<td>Dysphoria</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td></td>
<td>Respiratory depression</td>
</tr>
<tr>
<td>Sedation</td>
<td></td>
<td>Sedation</td>
</tr>
<tr>
<td>Miosis</td>
<td></td>
<td>Miosis</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary retention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dependence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tolerance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature increase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradycardia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side Effect</td>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td>---------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>1. Dilute one ampule of naloxone (0.4mg/cc) in 10 cc normal saline. Administer 1 cc (0.04mg) every minute until respiration are &gt; 8/minute. This technique prevents the reversal of the pain relief.</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>1. Scopolamine patch every 72 hours. (Use 1/2 of a patch if age greater than 60). 2. If above fails, add Metoclopramide 10 mg every 6 hours. 3. If above fails, add Odansetron 2-4 mg every 8 hours. 4. If #3 fails, replace with Prochlorperazine 5-10 mg every 6 hours or Trimethobenzamide 100-250 mg every 6 hours or Hydroxyzine 50-100 mg every 6 hours. 5. If #4 fails replace with Diphenhydramine 25-50 mg every 6 hours. 6. If #5 fails, decrease opioid. If this fails, discontinue opioid and refer to pain specialist.</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>Prophylactic bowel maintenance program</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. Metamucil, 1 tablespoon each morning in juice. 2. Prune juice twice daily. 3. Senokot-S, 2 tablets at bedtime. 4. Encourage fluids. 5. If no BM in any 48 hour period: -Milk of Magnesia, 30 cc orally -Dulcolax, 10 mg orally at bedtime -Fleets enema 6. If patient is on antacids, choose Mylanta or Maalox.</td>
<td></td>
</tr>
<tr>
<td>Pruritis</td>
<td>1. Diphenhydramine 25-50 mg every 6 hours.</td>
<td></td>
</tr>
</tbody>
</table>
Table 3.4 Signs and symptoms of opioid withdrawal

<table>
<thead>
<tr>
<th>Hours after last dose</th>
<th>Signs and symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-12</td>
<td>Lacrimation, Rhinorrhea, Yawning, Sweating</td>
</tr>
<tr>
<td>18-20</td>
<td>Dilated pupils, Anorexia, Gooseflesh, Tremors, Restlessness, Irritability, Anxiety</td>
</tr>
<tr>
<td>48-72</td>
<td>Increased irritability, Insomnia, Marked anorexia, Violent yawning, Severe sneezing, Muscle spasms, Generalized body aches, Nausea and vomiting, Diarrhea, Abdominal cramping, Increased heart rate, Increased blood pressure, Chills and hyperthermia, Flushing, Low back pain, Hyperpnea</td>
</tr>
</tbody>
</table>

Table 3.5 Equianalgesic doses of commonly used opioids

<table>
<thead>
<tr>
<th>DRUG</th>
<th>EQUIANALGESIC DOSE (MG)</th>
<th>PARENTERAL:ORAL DOSE RATIO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IV</td>
<td>PO</td>
</tr>
<tr>
<td>Morphine</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>Codeine</td>
<td>120</td>
<td>200</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Hydrocodone</td>
<td></td>
<td>30</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1.5</td>
<td>7.5</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Meperidine</td>
<td>75</td>
<td>300</td>
</tr>
<tr>
<td>Methadone</td>
<td>10</td>
<td>12.5</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>130</td>
<td></td>
</tr>
<tr>
<td>Butorphanol</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Pentazocine</td>
<td>30</td>
<td>150</td>
</tr>
</tbody>
</table>
Table 3.6 Commonly used opioids

<table>
<thead>
<tr>
<th>Agonists</th>
<th>Agonist-antagonists</th>
<th>Antagonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Butorphanol</td>
<td>Naloxone</td>
</tr>
<tr>
<td>Codeine</td>
<td>Buprenorphine</td>
<td>Naltrexone</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Nalbuphine</td>
<td></td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>Pentazocine</td>
<td></td>
</tr>
<tr>
<td>Hydromorphone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levorphanol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meperidine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxymorphone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propoxyphene</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 3.7 Guidelines for the Management of Opioid Therapy for NonMalignant Pain

1. A trial of opioids should be considered after all other reasonable attempts at analgesia have failed.
2. A comprehensive medical history and physical examination should be documented.
3. A trial of opioids does not imply a "last resort" or giving up on the patient and this should be communicated to the patient.
4. A history of substance abuse (including alcohol abuse), severe character pathology or chaotic home environments are relative contraindications. If opioids are initiated in this group, it should be undertaken cautiously, with careful monitoring. Evaluation and advice by a pain specialist should be considered in this population of patients.
5. A single practitioner should assume primary responsibility for treatment.
6. A verbal or written "contract" should be established with the patient. This agreement should include the possibility of the practitioner weaning the opioid if addictive behavior develops such as non-compliance, dose-escalation, social breakdown, etc.
7. The patient should be provided an informed, verbal or written consent before starting therapy. Points to be covered include recognition of the low risk of true addiction, potential cognitive impairment, likelihood of physical dependence.
8. After drug selection, doses should be given on an around-the-clock basis and titrated to effect.
9. Failure to achieve at least partial analgesia at relatively low initial doses in the nontolerant patient raises questions about the potential treatability of the pain syndrome with opioids.
10. Emphasis should be given to capitalize on improved analgesia by gains in physical and social function.
11. The physician may permit additional doses of the opioid on top of the daily dose in times of increased pain only if tightly controlled and limited.
12. Initially, patients must be seen and drugs prescribed at least monthly and their progress documented. When stable, less frequent visits may be acceptable.
13. At each visit, assessment and documentation should specifically address:
   a. Comfort (degree of analgesia)
   b. Opioid-related side effects
   c. Functional status (physical and psychosocial)
   d. Existence of aberrant drug-related behaviors
   e. Mood
Table 3.9 Guidelines for Intravenous Patient Controlled Analgesia

1. Request consult for intravenous line placement, either central or peripheral with a subcutaneous access port.
2. Convert the total daily opioid dose to and intravenous dose (refer to Table 3.5).
3. Take two-thirds of this total dose and administer over 24 hours as a continuous infusion. The patient will titrate in the remaining one-third by using the IVPCA bolus dosing. The typical bolus dosing is as follows:

   - Morphine: bolus dose = 1-5mg  lockout = 8-12 minutes
   - Hydromorphone: bolus dose = 0.2-1mg  lockout = 8-12 minutes

4. If the patient is requiring frequent bolus dosing, increase the basal infusion by 10-20% per day and the bolus dosing by 10-20% per day until comfortable.
5. If the patient is experiencing unacceptable side effects, decrease the basal infusion and bolus dosing by 10-20% per day until side effects resolve.

Case scenario:

Mr. X suffers from pain secondary to metastatic lung CA to his lumbar spine. He is requiring 900 mg per day of morphine and in spite of good pain relief, he is experiencing frequent breakthrough pain. The decision to start IVPCA is made and a peripheral intravenous line with a subcutaneous port is placed. The conversion is as follows:

   a. 900 mg oral morphine/3 = 300 mg IV morphine
   b. two-thirds of 300mg = 200 mg morphine to be administered continuously over 24 hours which = 8mg per hour
   c. the bolus dose is 2 mg with a 10 minute lockout

The dose is slowly titrated up to an infusion rate of 15 mg per hour and a 5 mg bolus dose for a total of 600 mg per day of morphine however the patient continues to suffer from pain. The decision is made to convert to the more potent opioid hydromorphone. The conversion is as follows:

   a. 600 mg IV morphine/6 = 100 mg IV hydromorphone
   b. two-thirds of 100 mg = 66 mg hydromorphone to be administered continuously over 24 hours which = 2.7 mg per hour
   c. the bolus dose is 0.5 mg with a 10 minute lockout.

This regimen is slowly titrated up and pain relief is achieved.
Non-Opioid Analgesics

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

The NSAIDs are a class of non-opioid analgesics which have anti-inflammatory, antipyretic, and analgesic properties. They are recommended for the relief of mild to moderate pain however depending on the mechanism behind the pain, the NSAIDs can be quite effective. If there is a strong inflammatory component to the pain, the NSAIDs can provide potent pain relief (i.e. bone pain). The analgesic actions of the NSAIDs are very similar across drugs but can differ greatly in duration of action. For moderate to severe pain, the NSAIDs are commonly combined with opioids. The NSAIDs are classified according to the parent compound from which they are derived (Table 4.1). If the patient fails to obtain pain relief from an NSAID, an NSAID from a different class should be tried rather than one from the same class. If an NSAID from each class has failed, it is unlikely that the patient will obtain pain relief from these.

**Mechanism of action** - The NSAID's mechanism of action is through the inhibition of cyclooxygenase by acetylation of this enzyme and preventing the production of prostaglandins. The breakdown of arachadonic acid by the enzyme cyclooxygenase results in the production of prostaglandins. These prostaglandins induce inflammation and directly sensitize the peripheral terminals of C fibers to thermal, mechanical and chemical stimuli. Because of this sensitization, the chemical mediators such as bradykinin, histamine, and substance P exert a greater effect on the pain receptors.

**Side effects** - Unfortunately, the NSAIDs have side effects which may greatly limit their use. These side effects are divided into gastrointestinal, hematological and renal (Table 4.2). All are directly related to the inhibition of prostaglandin synthesis. As a group, the non-acetylated salicylates (Table 4.1) are less likely to cause these side effects.

NSAIDs cause a localized irritation of the gastric mucosa from a direct effect. Higher doses may cause erosive gastritis and gastric hemorrhage secondary to a decrease in PGE2 and PG12. PGE2 and PG12 both inhibit gastric acid secretion and stimulate cytoprotective intestinal mucus. A history of peptic ulcer disease and/or gastric bleeding, use of alcohol, increasing age and high doses of NSAIDs are risk factors to developing gastropathy from NSAID use. The use of prophylaxis for NSAID-induced gastropathy is controversial. The H2-antagonists- and prostaglandin analogues (misoprostol) have been used with varying success. The physician must weigh the n benefits. If the patient is obtaining good pain relief in the presence of gastropathy, it may be wise to continue the NSAIDs and add a prophylaxis.

With the exception of aspirin, all of the NSAIDs reversibly inhibit platelet aggregation. Normal hemostasis is restored after 5 half-lives which is the time required for the body to clear all of the drug. Aspirin irreversibly inhibits platelet aggregation and thus lasts for the life of the platelets (6-10 days). The varying effect of the NSAIDs on platelet function depends on the balance between the inhibition, of thromboxane A2 and
synthesis within the platelets and inhibition of prostacyclin synthesis within the endothelial cells. Thromboxane A2 stimulates and prostacyclin inhibits platelet aggregation. As NSAIDs will inhibit the synthesis of both of these prostaglandins, the net balance determines the effect of each NSAID on platelet function. For instance, the non-acetylated salicylates have less of an effect on platelet function than the other NSAIDs in different classes. Because of their antiplatelet effect, the NSAIDs should be used with caution in patients with underlying bleeding problems (i.e. on anticoagulant therapy). If an NSAID must be used in patients with a bleeding disorder, a short acting drug should be used (Table 1).

Nephrotoxicity from NSAIDs is rare in the healthy patient because renal blood flow and glomerular filtration are not prostaglandin-dependent. However, in patients who are volume depleted or have congestive heart failure or hepatic cirrhosis, the risk of nephrotoxicity from the NSAIDs increases. This increased risk occurs because these conditions activate the rennin-angiotensin system and sympathetic nervous system which in turn promote local secretion of vasodilator prostaglandins. These vasodilator prostaglandins minimize the renal ischemia produced by these syndromes. The NSAIDs inhibit these prostaglandins which may lead to decreased renal perfusion and glomerular filtration. The nephrotoxicity is manifested by hematuria, proteinuria, and nephrotic syndrome. Sodium and water retention may also occur in the presence of congestive heart failure, hepatic cirrhosis, and volume depletion because the prostaglandins inhibit tubular reabsorption of sodium and water. Therefore, the prostaglandin inhibition produced by the NSAIDs may lead to fluid retention, impaired responsiveness to diuretic therapy, and hyperkalemia.

There are rare idiosyncratic reactions to NSAIDs which are not related to prostaglandin inhibition. These reactions are reviewed in Table 4.2. Although they may be serious, they are very rare.

**Pharmacology** - All of the NSAIDs have a high oral bio-availability (80-100%) and are rapidly absorbed from the gastrointestinal tract. Ketorolac is the only NSAID approved for IM or IV use. The NSAIDs have a low volume of distribution due to their high protein binding (80-99 %). One would assume that the half life of the NSAIDs are short because of the low volume of distribution, however, some can be quite long (Table 4.1). This is because the enzymes involved in the biotransformation of the NSAIDs are saturatable, and the elimination half life will increase with increased dose. The NSAIDs are metabolized by the liver by oxidation and conjugation. The conjugated and oxidized products are then eliminated by the kidney.

**Topical Formulations:**

**Flector patch** (diclofenac epolamine topical patch) 1.3% is an adhesive patch applied to intact skin. Dosing instructions are to apply one patch over the painful joint or area for 12 hours, then replace with a new patch every 12 hours. Following a single application of the Flector patch, peak plasma concentrations of diclofenac range 0.7 – 6 ng/mL at 10 – 20 hours after application. Systemic exposure and maximum plasma concentrations of diclofenac, after repeated dosing for four days with Flector patch, were lower (<1%) than
after a single oral 50-mg diclofenac sodium tablet. The plasma elimination half-life of diclofenac after application of Flector Patch is approximately 12 hours. Although systemic concentrations are much lower than oral delivery, the effect on clinical risks are unknown. Therefore, Flector patch carries the same warnings as oral NSAIDs including increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke especially in the first 10-14 days following CABG surgery, risk of hypertension, fluid retention, gastrointestinal inflammation/bleeding/ulceration/perforation, renal papillary necrosis/injury, and hepatotoxicity. Finally, as with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to Flector Patch, and it should not be given to patients with the aspirin triad.

Voltaren Gel (diclofenac sodium topical gel) 1%. Voltaren gel is a topical ointment indicated for the relief of the pain of osteoarthritis of joints. Voltaren gel is applied 2g/QID per upper extremity joint, 4g/QID per lower extremity joint, not to exceed 32 grams per day over all affected joints. Systemic exposure and maximum plasma concentrations of diclofenac are significantly lower with Voltaren Gel than with comparable oral treatment of diclofenac sodium. Systemic exposure with recommended use of Voltaren Gel (4 x 4 g per day) is on average 17 times lower than with oral treatment. The amount of diclofenac sodium that is systemically absorbed from Voltaren Gel is on average 6% of the systemic exposure from an oral form of diclofenac sodium. The average peak plasma concentration with recommended use of Voltaren Gel (4 x 4 g per day) is 158 times lower than with the oral treatment. Never the less, Voltaren gel carries the same warnings as other NSAIDs including topical flector patch including cardiovascular risk, gastrointestinal adverse events, anaphylaxis risk, hypertension, renal and hepatic injury.

COX-2 Inhibitors
Like the NSAIDs, the COX-2 inhibitors are anti-inflammatory drugs. They are specific to the COX-2 enzyme inhibition; therefore, they have less GI and platelet effects. Like the NSAIDs, they have renal effects. The COX-2 enzyme is expressed constitutively in the brain and kidneys but is inducible in other tissues. The COX-1 enzyme is expressed constitutively in all tissues. In times of injury or stress, the COX-2 enzyme is induced which can lead to pain and inflammation. Even in the absence of pain impulses into the CNS, COX-2 can be induced through circulating interleukins. COX-2 inhibitors appear to have an increase risk of cardiovascular and thromboembolic events. This risk occurs in patients that are already at risk for these events and with preexisting disease. Patients without underlying disease are not at risk. Rofecoxib and valdecoxib were removed from the market because of a significantly greater risk over celecoxib. Both Celebrex and Vioxx have a sulfa base and should be avoided in patients with sulfa allergies.

Acetaminophen
Acetaminophen is a para-aminophenol derivative which differs from the NSAIDs because of its lack of anti-inflammatory properties. It is appropriate for mild to moderate pain relief when an anti-inflammatory effect is not necessary. It is commonly combined with narcotics.
Mechanism of Action - The mechanism of action of acetaminophen is unknown. It may produce its analgesia by nitric oxide synthase inhibition in the spinal cord. Nitric oxide is a neurotransmitter which is released in the spinal cord dorsal horn when C fibers are activated. The presence of nitric oxide in the synaptic cleft can activate post synaptic spinothalamic tract neurons. Acetaminophen does inhibit brain cyclooxygenase which may account for its antipyretic activity.

Side effects - The side effects of acetaminophen are minimal. It does not have the GI irritation or the platelet inhibition that the NSAIDs have. The major serious side effect is hepatic necrosis which can occur with large doses of acetaminophen (10-15 gms). However, with chronic acetaminophen use, the total daily dose required for hepatic toxicity may be lower than the acute dose. The hepatic necrosis results from the formation of N-acetyl-benzoquinoneimine which reacts with glutathione and sulfhydryl groups of proteins. The treatment of this toxicity is acetylcysteine which binds to N-acetyl-benzoquinoneimine and inactivates it. There are many opioid-acetaminophen combinations which were developed for acute pain management and not for chronic use. Because of the triplicate system in many states, there has been an inappropriate use of these opioid-acetaminophen combinations which has resulted in many cases of liver toxicity. Many of the opioid-acetaminophen combinations are not required to be dispensed on triplicate forms, therefore, many physicians use these preparations to avoid the use of triplicates. If the chronic pain syndrome cannot be managed with < 8/day of the opioid/acetaminophen combinations, then a non-acetaminophen containing opioid is recommended.

Pharmacology - The pharmacology of acetaminophen is very similar to the NSAIDs with the exception of a larger volume of distribution due to its low protein binding (20%). Acetaminophen is metabolized by the liver and eliminated by the kidney.

Tramadol - Tramadol hydrochloride is a drug that has been in use in Germany to provide pain relief since the late 1970s. This drug is now available in 70 countries throughout the world. This drug became available in the United States in early 1995. Tramadol hydrochloride is a transisomeric form of a phenyl substituted aminomethylcyclohexanol. It is produced as a racemic mixture of two optically active enantiomers designated (+) and (-) tramadol.

Mechanism of Action - Tramadol produces analgesia through two mechanisms. One mechanism relates to its weak affinity for mu opioid receptors (about 6000-fold less than morphine, about 100-fold less than d-propoxyphene, and about the same as dextromethorphan (anti-tussive found in cough syrups, see chapter on opioid pharmacology). Therefore it is an extremely weak opioid agonist. An active metabolite (O-desmethyltramadol) binds to opioid receptors with a greater affinity than the parent compound and might contribute to this component. However, clinical trials suggest that the primary analgesic action of tramadol is mediated through nonopioid mechanism(s). This nonopioid mechanism appears related to the ability of tramadol to enhance the
release or inhibit the neuronal reuptake of the central monoamine neurotransmitters 5-hydroxytryptamine (serotonin) and norepinephrine. Several lines of evidence suggest that the two mechanisms of action of tramadol combine synergistically to produce analgesia (see chapter on co-analgesics, antidepressants).

**Side effects** - The most common side effects include nausea, somnolence, dizziness, vomiting and headache. In long-term trials, nausea has been the most common side effect. Side effects are reduced if lower doses are used upon initiating the drug. The side effects of Tramadol are similar in type but not frequency to the weak opioids and antidepressants. There are no serious side effects. There is no evidence of euphoria, abuse, dose escalation, spontaneous withdrawal, or naloxone-induced withdrawal.

**Pharmacology** - Tramadol is readily absorbed from the gastrointestinal tract with only 20% protein bound. Tramadol is metabolized by the liver and the metabolites are excreted by the kidney. The onset of analgesia is slightly longer than weak opioids but the duration of action is longer.

**Recommended Dosing** - The proposed recommended dose of tramadol in adults will be 50 - 100 mg as needed every 4 to 6 hours. The total daily dose should not exceed 400 mg in persons with normal renal and hepatic function. In otherwise healthy elderly patients up to age 75 years, dose adjustments are not needed. In individuals older than 75 years, the total daily dose should be decreased to 300 mg. In renal impaired patients, the dose of tramadol should be 50 - 100 mg every 12 hours. In patients with advanced cirrhosis, the recommended dose is 50 mg every 12 hours.

**Suggested Reading**


### Table 4.1 Classification of the Nonsteroidal Antiinflammatory Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half-life (hrs.)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carboxylic Acids</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Salicylic Acids</strong></td>
<td></td>
</tr>
<tr>
<td>Acetylsalicylic acid (Aspirin)</td>
<td>4-15</td>
</tr>
<tr>
<td>Non-acetylated salicylates</td>
<td></td>
</tr>
<tr>
<td>Choline Magnesium Trisalicylate</td>
<td>4-15</td>
</tr>
<tr>
<td>Salicyl salicylate</td>
<td>4-15</td>
</tr>
<tr>
<td>Diflunisal</td>
<td>7-15</td>
</tr>
<tr>
<td><strong>Acetic Acids</strong></td>
<td></td>
</tr>
<tr>
<td>Indoles</td>
<td></td>
</tr>
<tr>
<td>Indomethacin</td>
<td>3-11</td>
</tr>
<tr>
<td>Sulindac</td>
<td>16</td>
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<tr>
<td>Pyrolle acetic acids</td>
<td></td>
</tr>
<tr>
<td>Tolmentin</td>
<td>1-2</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>3-8</td>
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<tr>
<td>Phenyl acetic acids</td>
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<tr>
<td>Diclofenac</td>
<td>2</td>
</tr>
<tr>
<td><strong>Propionic Acids</strong></td>
<td></td>
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<tr>
<td>Phenylpropionic acids</td>
<td></td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>2</td>
</tr>
<tr>
<td>Fenoprofen</td>
<td>2</td>
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<tr>
<td>Flurbiprofen</td>
<td>3-4</td>
</tr>
<tr>
<td>Ketoprofen</td>
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</tr>
<tr>
<td>Naphthylpropionic acids</td>
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<tr>
<td>Narpoxen</td>
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<tr>
<td><strong>Anthranilic Acids</strong></td>
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<tr>
<td>Fenamates</td>
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<tr>
<td>Meclofenamate</td>
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<tr>
<td><strong>Pyrazoles</strong></td>
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<tr>
<td>Phenylbutazone</td>
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<tr>
<td><strong>Oxicams</strong></td>
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<tr>
<td>Piroxicam</td>
<td>30-86</td>
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<tr>
<td>Gastrointestinal</td>
<td>Hematologic</td>
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<tr>
<td>GI Upset</td>
<td>Platelet inhibition</td>
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<tr>
<td>Gastritis</td>
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COANALGESICS

The co-analgesics are drugs used in pain management which may or may not have intrinsic analgesic properties. However, they provide pain relief in certain pain syndromes or potentiate the common analgesics such as opioids. All of the co-analgesics used in pain management were originally developed for treatment of certain disease other than pain. As we have developed a greater understanding of the physiology behind pain syndromes, there has been increasing use of these co-analgesics for pain. In fact, in many circumstances, the co-analgesics are the treatment of choice instead of the opioids and non-opioid analgesics. When administering these co-analgesics, the practitioner must make it clear to the patient why these drugs are being used. Often there is confusion among the patients and pharmacists because the use of these drugs for pain therapy is not in the master drug file. This chapter will present the commonly used co-analgesics.

ANTIDEPRESSANTS

The antidepressants are commonly used in certain chronic pain syndromes for pain relief. The analgesic doses are lower than the antidepressant doses. Whether the antidepressants actually treat underlying depression (which is known to exacerbate chronic pain) with a corresponding decrease in pain is unknown. However, it appears that these drugs have a direct effect on certain painful conditions. Pain syndromes that have been shown to respond to antidepressants are postherpetic neuralgia, diabetic neuropathy, tension headache, migraine headache, and atypical facial pain. However, most neuropathic pain syndromes (see definitions chapter one) respond to the antidepressants. The antidepressants are most effective for diffuse, burning, and dysesthetic pain. Most patients can be managed at or below antidepressant doses. However, some patients may require antidepressant levels in which case, blood levels should be monitored.

Mechanism of action

The antidepressants inhibit the reuptake of biogenic amines (norepinephrine and serotonin) into the nerve terminals which results in an increase in the concentration and duration of action of the neurotransmitters at the synapse. Both serotonergic and noradrenergic neurons in the brainstem project to and inhibit C fiber input into the spinal cord. The antidepressants are thought to activate these descending inhibitory neurons. As discussed in the opioid pharmacology section, the opioids also activate these brainstem inhibitory neurons and the antidepressants potentiate the action of the serotonin and norepinephrine released by the opioids. The antidepressants also have alpha 1 blocking activity which may account for some of the pain relief in neuropathic pain (see below under alpha 1 blockers and alpha 2 agonists). It has recently been shown that the antidepressants have intrinsic NMDA antagonist activity (see chapter on anatomy and physiology of pain pathways and final chapter on the future in pain management) which may account for their action on neuropathic pain.

Side effects

The antidepressants have anticholinergic, antihistaminic, antidopaminergic, and alpha 1 blocking activity Table 5.1. Because of this activity, the following side effects may occur:
1) anticholinergic side effects - dry mouth, constipation, urinary retention, sedation.
2) antihistaminic side effects - sedation
3) alpha 1 blockade - orthostatic hypotension
4) antidopaminergic - dystonia

The sedation seen with the antidepressants may be advantageous as many chronic pain patients suffer from insomnia. Because of this side effect, the drug is usually administered at bedtime. If a pain patient suffers from insomnia it is best to use an antidepressant with more sedating properties such as amitriptyline or doxepin. The antidepressants with fewer anticholinergic effects (i.e. trazadone and nortriptyline) are less sedating and useful in patients that do not suffer from insomnia. The antidepressants also cause depression of cardiac excitability and therefore may result in cardiac conduction defects.

**Pharmacology**

The antidepressants are well absorbed from the gastrointestinal tract and have very long half-lifes and thus can be given in single daily doses. They are metabolized by the liver and the tertiary amines, imipramine and amitriptyline, are demethylated to desipramine and nortriptyline respectively.

**Drug Monograms**

The antidepressants are divided into the tricyclics, serotonin specific reuptake inhibitors and the atypical antidepressants. Table 5.2 gives a summary of the antidepressants commonly used in pain management.

**Tricyclics**

The tricyclics are the oldest of the antidepressants. Unfortunately, they have the highest side effect profile. Because of this, they are generally administered as a single bedtime dose. In general, for patients over 65, the initial starting dose is 10 mg at bedtime and increased by 10 mg as tolerated. For patients under 65, the initial starting dose is 25 mg and increased by 25 mg as tolerated. Most of the tricyclics are available in elixir form.

**Amitriptyline** - This is the most commonly used antidepressant for pain management. The efficacy of this drug has been proven in many clinical studies. It is a tricyclic which inhibits the reuptake of both serotonin and norepinephrine. Unfortunately, it has a potent side effect profile because of the anticholinergic, antihistaminic, and alpha adrenergic blockade.

**Nortriptyline** - This drug is a major metabolite of amitriptyline and is therefore classified as a secondary amine. Although the antidepressant effect occurs within a therapeutic window, the pain relieving properties does not. It primarily inhibits the reuptake of norepinephrine. It has a lower side effect profile than amitriptyline.
**Imipramine** - This drug blocks the reuptake of both serotonin and norepinephrine (norepinephrine more than serotonin). It side effect profile falls between amitriptyline and nortriptyline. It is used in psychiatry to treat anxiety disorders and thus may be helpful in pain patients that suffer from anxiety.

**Desipramine** - This drug is the active metabolite of imipramine. It blocks the reuptake of serotonin and norepinephrine (norepinephrine more than serotonin). It has a low side effect profile. It may actually stimulate some patients.

**Doxepin** - This drug has a side effect profile slightly less than amitriptyline. It has antihistaminic effects comparable to cimetidine.

**Amoxapine** - In addition to inhibiting norepinephrine and serotonin reuptake, this drug is antidopaminergic. This is explained by its close structural relationship to the neuroleptic drugs. It has a high incidence of producing seizures in the overdose situation. It has also been associated with neuroleptic malignant syndrome.

**Selective Norepinephrine Reuptake Inhibitors (SNRIs)**

The SNRIs are a new class of antidepressants that selectively inhibit the reuptake of norepinephrine. Norepinephrine reuptake inhibition is more specific for pain management than serotonin reuptake inhibition. Because they lack the anticholinergic effects seen with the TCAs, they have fewer side effects.

**Duloxetine** – this drug is FDA approved for the treatment of neuropathic pain related to diabetes and fibromyalgia. There is an NDA on file with the FDA for an indication for the treatment of fibromyalgia. Unlike all other antidepressants, Duloxetine has a rapid onset of action with analgesia occurring within the first week of therapy unlike the other agents which take up to 8 weeks. The most common side effect is nausea and there is a contraindication if the patient has preexisting liver disease.

**Venlafaxine** – This drug has a good side effect profile but the onset of action is up to 6 weeks more like the TCAs.

**Serotonin Specific Reuptake Inhibitors (SSRIs)**

The SSRIs are a class of antidepressant which are selectively inhibits the reuptake of serotonin. They have minimal side effects when compared to other antidepressants. They have not been around long enough to demonstrate absolute effectiveness in pain management but they do appear to have a role in this area. They are generally stimulating and therefore given in the morning. It is not uncommon to administer an SSRI in the morning and a tricyclic in the evening.

**Fluoxetine** - This drug has been inappropriately blasted by the lay press. It has minimal side effects other than occasional anxiety and nausea. It may lessen the frequency of migraine headache attacks.
Paroxetine - Both sedation and insomnia have been reported with this drug. Nausea, sweating, dizziness, weakness, diarrhea, constipation and ejaculatory disturbances have also been reported.

Sertraline - This is a newer antidepressant which lacks many of the side effects of the tricyclics. The efficacy of Sertraline in chronic pain management is unknown.

Atypical Antidepressants
   These are non-tricyclic drugs which are chemically unrelated to the classic tricyclic structure.

Trazadone - This drug has a relative lack of antidepressant side effects. It is mildly sedating and is given in doses twice that of the tricyclics. It has been associated with priapism.

Maprotiline - This drug has relatively few anticholinergic side effects and lower incidence of cardiovascular side effects. It has been reported to cause seizures in normal doses.

Venlafaxine - The efficacy of this drug in chronic pain management is unknown.

Guidelines for the Antidepressants
   Duloxetine is the antidepressant of choice. It can be started as a bedtime dose and titrated up to 60 mg at bedtime. It is generally well tolerated.

   Because of the side effects of the antidepressants (especially the tricyclics), patient compliance may be poor. The most common cause of non-compliance with the tricyclics is starting an initial dose that is too high. It is best to start at the smallest dose possible and gradually increase slowly over 2-4 weeks. The choice of the tricyclic will depend on the patients sleep disturbance. If the patient suffers from a sleep disturbance, a more sedating tricyclic will be necessary. If there is no sleep disturbance, a less sedating tricyclic will be the drug of choice (Table 5.2). Some patients may benefit from the stimulating effect of the SSRIs in the morning and the sedative effect of the tricyclics in the evening, therefore, these drugs may be given together.

   Therapeutic serum levels of the antidepressants that apply for depression do not apply for pain management; therefore, serum levels are usually not necessary. However, if the total dose is greater than 100 mg daily, serum levels may be necessary to avoid toxic levels.

ANTICONVULSANTS
   The anticonvulsant drugs have been demonstrated to be effective in pain syndromes with an intermittent lancinating quality. The anticonvulsants most commonly used in chronic pain management include gabapentin and pregabalin. Gabapentin is FDA approved for the treatment of postherpetic neuralgia. Pregabalin is FDA approved for the treatment of pain related to diabetic neuropathy, postherpetic neuralgia and fibromyalgia. Lamotrigine,
Oxcarbazepine, carbamazepine, phenytoin, and valproic acid have been used in chronic pain with mixed results. Conditions that have been shown to be responsive to the anticonvulsants include trigeminal neuralgia, glossopharyngeal neuralgia, paroxysmal pains of multiple sclerosis, diabetic neuropathy, and miscellaneous lancinating pains (postlaminectomy, postamputation, and postherpetic neuralgia). They are generally started at low doses and gradually increased until the emergence of toxicity or intolerable side effects. The "therapeutic" serum levels that apply for the treatment of epilepsy do not apply for pain management. Therefore the drugs should be titrated to pain relief and side effects. Table 5.3 lists the commonly used anticonvulsants used in pain management.

**Guidelines for the Anticonvulsants**

With the exception of gabapentin and pregabalin, baseline liver function tests and a CBC is necessary prior to starting the anticonvulsants. If the LFTs are elevated, it is wise to try gabapentin or pregablin only. Initially start the drug at the lowest dose twice a day and slowly increase over 2-4 weeks. If side effects occur, decrease the dose. Therapeutic levels that apply for the antiseizure activity do not apply for pain relief. Liver function tests and a CBC should be monitored monthly for the first few months. If they remain stable then they may be checked every 3-6 months. If these studies are abnormal, it is suggested that the medication be discontinued.

Gabapentin and pregablin are unique in that it is not necessary to monitor blood levels or liver functions during therapy. Gabapentin and pregablin has no known systemic toxicities nor have therapeutic blood levels been established. Side effects that may occur include sedation and ataxia which in most cases will subside within two weeks. Peripheral edema and weight gain can also be a problem. The recommended starting dose of gabapentin is 300mg TID and may be increased up to 1800 mg/day. Doses as high as 3600mg/day have been reported in seizure therapy with no serious side effects. For pregablin, the recommended starting dose is 75 mg BID up to 600 mg/day.

**ANTIARRHYTHMICS**

Some of the antiarrhythmics have been shown to affect certain chronic pain syndromes (Table 5.5) however, studies have been mixed and inconsistent. These drugs work much the same way as the anticonvulsants in that they are effective in treating pain which is intermittent and lancinating. However, they are also effective in pain which has an allodynic and dysesthetic component. Bretylium and Guanethidine are used in the treatment of sympathetically maintained pain. These two drugs should be reserved for physicians experienced in pain management as they are used in intravenous regional blockade which is a procedure performed by pain specialists. Guanethidine is not approved for use in the United States. Lidocaine is available in an intravenous form only and is used for diagnostic and therapeutic purposes. Intravenous lidocaine infusions have been used to determine if the pain syndrome is responsive to the membrane stabilizers such as the anticonvulsants and antiarrhythmics. Because of the severe toxicities that can result from intravenous lidocaine, this procedure should be reserved for specially trained physicians. The only two antiarrhythmics used orally for chronic pain include mexiletine and tocainide. Mexiletine, tocainide and lidocaine are used to treat the same syndromes that are responsive to the anticonvulsants.
**Mechanism of Action**

**Mexiletine, Tocainide,** and Lidocaine - These drugs appear to act on ectopic foci in damaged nerves much the same way as the anticonvulsants. They suppress the abnormal activity in peripheral nerves through sodium channel blockade. The concentrations required to suppress ectopic foci and abnormal activity is far below that required for frank nerve conduction blockade.

**Bretylium and Guanethidine** - Both of these drugs act by inhibiting the release of norepinephrine from the postganglionic adrenergic neurons. Because of this action, they produce a chemical sympathectomy. Bretylium lasts from 12-24 hours whereas guanethidine lasts from 24-72 hours. The chemical sympathectomy produced by these drugs decreases the pain associated with sympathetically maintained pain (See chapter 1, definitions and clinical section). They are also diagnostic for this syndrome.

**Side Effects**

The side effects differ between the antiarrhythmics because they are chemically unrelated (Table 5.6).

Nausea and vomiting may occur with all of the antiarrhythmics. It is commonly seen in IV regional blockade with bretylium after the tourniquet is deflated. It is also common with mexiletine if the dose of this drug is increased too rapidly. A slow increase over a couple of weeks up to a maximum of 10mg/kg/day will prevent this side effect.

Tremors and irritability may occur with mexiletine especially in older patients. This side effect usually disappears if the dose is decreased.

Seizures may occur with lidocaine, mexiletine and tocainide if given in high enough doses. However, this is extremely rare in the dosage range used for chronic pain management.

**Guidelines for the Antiarrhythmics**

The most commonly used antiarrhythmic for pain is mexiletine. This drug should be started at the lowest dose possible twice a day. Slowly increase the drug over 2-4 weeks up to a maximum of 10 mg/kg/day. If side effects occur, decrease the dose. Therapeutic serum levels that apply to the antiarrhythmic effect of this drug do not apply to pain relief, therefore, serum levels are usually not necessary.

If the patient is on other cardiac drugs or has a history of congestive heart failure, a consultation with a cardiologist should be sought prior to starting this drug.

**ALPHA-1 ANTAGONISTS AND ALPHA-2 AGONISTS**

The sympathetic nervous system (SNS) is involved in many chronic pain syndromes. If it is determined that the SNS is involved in the pain problem, then
medications can be administered to alter the SNS. The alpha blockers and alpha-2 agonists are used for this purpose. The commonly used alpha receptor agonists and antagonists are given in Table 5.6.

A phentolamine infusion has been used by pain specialists prior to starting oral prazosin, phenoxybenzamine, or clonidine. Routinely, 0.5-1 mg/kg of phentolamine is infused intravenously over 30 minutes until pain relief occurs or unacceptable tachycardia or hypotension occurs. If this infusion is successful, then a trial of this class of drugs may be beneficial. Another method of determining if the pain syndrome is sympathetically mediated is by blocking the sympathetic nerve supply to the painful area. This can be accomplished by blocking the stellate ganglion for upper extremity pain or the lumbar sympathetic ganglion for lower extremity pain.

**Mechanism of Action**

Peripheral nerve terminals possess alpha receptors which may become active in neuropathic pain conditions. The SNS releases norepinephrine which stimulates these receptors and leads to pain. The alpha blockers block the action of norepinephrine on these receptors and the alpha-2 agonists inhibit the release of norepinephrine from the postganglionic sympathetic nerve terminals. In this way, these drugs produce a chemical sympathectomy.

**Side effects**

Orthostatic hypotension is the most common side effect and may occur with both the alpha-1 antagonists and the alpha-2 agonists. The alpha receptors are also located on blood vessels where they increase vascular tone, therefore, if this response is inhibited, orthostasis results. As the body fluids shift to compensate for the change in vascular tone, this side effect usually disappears with time.

Due to its central effect, clonidine may result in sedation. This sedation usually disappears with time (Table 5.7).

**Guidelines for the Alpha-1 antagonists and Alpha-2 agonists**

These drugs are well tolerated with few side effects. These drugs must be titrated to blood pressure rather than pain relief. If unacceptable low blood pressure occurs before pain relief, then these drugs must be discontinued. If the patient will tolerate it, a combination of an alpha-1 antagonists and alpha-2-agonist may be tried. All of these drugs should be started at the lowest dose twice a day (once a day for terazosin) and increased slowly over 2-4 weeks. The maximum doses are: prazosin and terazosin 20 mg/day, phenoxybenzamine 40 mg/day, and clonidine 0.6 mg/day. Blood pressure should be monitored closely while initially titrating these drugs.

**Vanilloids**

**Capsaicin Cream** - Capsaicin is a derivative of red chili pepper which depletes substance P from C fiber terminals by blocking transport and synthesis. Initially, the cream may burn after application, however, this will disappear with continued use. As significant depletion of the substance P from the peripheral terminals takes up to three
weeks, treatment must be continued for this minimum period of time before efficacy can be gauged. Speed of onset and duration of analgesia depends on dose, duration, and frequency of exposure. The patient must use this cream 3-4 times per day in order for it to be effective. The topical application of low-dose capsaicin (<1%) is effective as an adjunct to the treatment of postherpetic neuralgia, postmastectomy pain, diabetic neuropathy, Myalgias, and joint pain. It is available in a 0.25% and 0.75% cream over-the-counter.

Mechanism of action: Capsaicin activates the transient receptor potential vanililloid 1 receptor (TRPV1) on unmyelinated C fiber nociceptors causing it to open. An influx of Ca++ and Na+ depolarize the nociceptive afferent terminals to release stored neuropeptides and are then desensitized. A biphasic desensitization response consists of early conduction block and delayed down regulation of TRPV1 receptors. In addition to unmyelinated C fiber nociceptors, TRPV1 receptors have been identified in visceral organs, spinal cord, and DRG.

**Qutenza (NGX-4010, a high-concentration (8%) capsaicin patch).** Qutenza is a new approach that has proven effective in the treatment of HIV-associated distal sensory polyneuropathy and postherpetic neuralgia. This treatment involves one 60 minute application of high dose capsaicin and requires topical and or oral analgesics for tolerance and provides pain relief for up to twelve weeks. Qutenza was approved by FDA in 2009 for treatment of postherpetic neuropathy and HIV-associated distal sensory polyneuropathy. Transient application site erythema (63%) and self-limited application site pain (42%) are the most common side effects.

**Resiniferatoxin.** Naturally occurring toxin from cactus-like plants Euphorbia resinifera. Resiniferatoxin has similar mechanism and higher potency compared to capsaicin. May produces a selective and irreversible deletion of the neurons that transmit chronic pain sensations when injected into the CSF. NIH is enrolling patients starting in 2010 for study of intrathecal administration for treatment of cancer pain.

**MISCELLANEOUS DRUGS**

There are a few miscellaneous drugs that can be utilized for chronic pain management. These drugs are less frequently used than those mentioned above, however in resistant cases, these drugs may be considered. Table 5.8 lists these drugs.

**Baclofen** - Baclofen is a GABA-B agonist which has antispasmodic activity. It is most commonly used for spasms that result from spinal cord injury. It has been shown to provide relief of pain that has a shooting or lancinating component. It also provides muscle relaxation. Baclofen has been recently approved for intrathecal use for the management of spasticity of spinal origin.

**Antihistamines** - As discussed in chapter two, histamine can activate C-fibers. Therefore, it seems reasonable to administer an antihistamine to block this C-fiber activation. Hydroxyzine is the only antihistamine which has been proven to have intrinsic analgesic activity of its own. Hydroxyzine potentiates the effects of narcotics and because
of this, it is commonly used in conjunction with these agents. Phenytoinoxamine and Orphenadrine have also been used in chronic pain management.

**Skeletal muscle relaxants** - The use of muscle relaxants are usually a part of a regimen and are rarely given alone. In conjunction with narcotics, NSAIDs and physical therapy, they can be quite effective in pain management. However, the long-term use of the skeletal muscle relaxants are controversial and not recommended at this time. The skeletal muscle relaxants are divided into the antispasmodics and centrally acting muscle relaxants.

The antispasmodics include Baclofen and Dantrolene. Baclofen is a muscle relaxant, antispasmodic which is mainly used for spasticity after spinal cord injury. It is now approved for intrathecal use in these patients. The antispasmodic effect of this drug is thought to be secondary to GABA-B activity at the spinal cord level. Baclofen may prove efficacious in pain secondary to muscle spasms and may also be used in intermittent lancinating pain. Dantrolene is a potent antispasmodic which dissociates the excitation-contraction coupling mechanism of skeletal muscle by interfering with the release of calcium from the sarcoplasmic reticulum. Fatal and non-fatal liver disorders may occur with Dantrolene, therefore, this drug should be used in selected cases only and therapy should be stopped if benefit is not evident by 45 days. The main indication for this drug is spasticity secondary to spinal cord injury.

The centrally acting muscle relaxants include Carisoprodol, Chlophenesin Carbamate, Chlorzoxazone, Cyclobenzaprine hydrochloride, Methocarbamol, and Orphenadrine citrate. Many of these are available in combination with certain other drugs.

**Calcium Channel Blockers** - The calcium channel blockers may be beneficial in the management of continuous burning pain. The drug of choice is nifedipine. The mechanism of action for pain relief is poorly understood.

**EMLA Cream** - EMLA (Eutectic Mixture of Local Anesthetic) is an emulsion of Lidocaine 2.5% and Prilocaine 2.5%. It was developed as a topical local anesthetic for intravenous cannulation in children. The efficacy of EMLA cream in pain management has not been studied, however, there are reports of effective treatment of superficial painful syndromes such as postherpetic neuralgia and superficial neuromas. Therefore, this may be a viable alternative in certain painful conditions.

**Sedative, hypnotics and tranquilizers** - The use of these drugs for chronic pain management is controversial. Despite this, their use in combination with opioids and antidepressants is not uncommon. In certain pain conditions where psychosis and anxiety are major symptoms, these drugs may prove useful. However, consultation with a psychiatrist may be indicated. Benzodiazepines often cause significant disturbances of REM sleep, tolerance and habituation can be a problem, and these drugs can be extremely difficult to withdraw. It is still unclear whether these drugs have intrinsic analgesic
activity. Because their use remains controversial, they should be used in selected cases only.

**Corticosteroids** - The corticosteroids have been proven efficacious in advanced cancer. They appear to provide short term analgesia by both a direct analgesic effect and secondary to tumor size reduction. Methylprednisolone and dexamethasone are the drugs of choice but other corticosteroids may be used. The corticosteroids may be useful in pain resulting from diffuse bony metastasis and tumor infiltration of neural structures such as the brachial plexus or lumbosacral plexus. Pain resulting from spinal cord compression has also been reported to be responsive to the corticosteroids. Another advantage of the corticosteroids is improvement of appetite and mood. The dosing of corticosteroids is empirical and should be individualized.

**Stimulants** - Cancer patients often obtain pain relief from high dose opioid therapy with the only side effect being sedation. The addition of a stimulant to their regimen can be very beneficial. Dextroamphetamine, Caffeine, and methylphenidate are the most commonly used. These drugs should be given in the morning will usually prevent daytime sedation induced by the opioids.

**Botulinum Toxin**
Botulinum toxin (BTX) has seven serotypes (A-G) which consist of a heavy chain bound to a light chain by a disulphide bond. The toxin heavy chain first binds to the nerve terminal and facilitates internalization of the light chain which then internally interferes with neurotransmitter vesicle docking on the plasma membrane required for release. The vesicular docking is mediated by the soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex which is the target for the BTX light chain. Normal nerve terminal function eventually recovers following BTX occurs by restoration of the SNARE complex.

Clinical application. BTX effectively inhibits muscle contraction by blocking presynaptic acetylcholine release from nerve terminals. It is effective for the treatment of migraine headaches, tension headaches, painful muscle spasticity and myofacial pain. By the same effect, BTX may be used on the autonomic nervous system to alleviate hyperhidrosis, hypersalivtion, or hyperlacrimation. Botulinum toxin –A has also been shown to have analgesic properties by inhibiting calcitonin gene-related peptide (CGRP) release from afferent nerve terminals, Substance P from dorsal root ganglia, and glutamate in the dorsal horn. BTX is too large to penetrate the blood brain barrier and is inactivated by retrograde axonal transport, therefore there is no direct central nervous system effect. In cancer patients, BTS has been shown to improve symptoms of radiation fibrosis syndrome. Its effect on neuropathic pain is also a potential approach for painful cancer conditions.

Clinical approach: Currently, three BTX products are approved for use in the United States: OnabotulinumtoxinA (Botox/Botox Cosmetic), AbobotulinumtoxinA (Dysport), and RimabotulinumtoxinB (Myobloc). Dosage units differ among the BTX products and are not comparable or convertible. BTX may be diluted in local anesthetic or sterile saline, and optimal dilutions have not been established for treatment of pain.
- **OnabotulinumtoxinA / Botox**
  - 100 units/vial for reconstitution
- **RimabotulinumtoxinB / Myobloc**
  - 5,000 U/mL
  - Diluted in 0.05% human serum albumin, 0.01 M sodium succinate, 0.1 M sodium chloride
  - 3.5 mL vials
- **AbobotulinumtoxinA / Dysport**
  - 300 U/vial and 500 U/vial
  - Reconstitute w 0.6 – 2.5 mL 0.9% sodium chloride (without preservative)

BTX is injected into striated muscle in increments of units. Paresis develops within five days and lasts several months. Therapy failure occurs secondary to the development of antibodies against BTX and is characterized by a spectrum from smaller effect and shorter duration to no effect.

**Botox Complications**

Complications include local effects such as muscle atrophy, dysphagia, dysphonia, ptosis, depending on site of injection. Systemic adverse reactions to BTX-A and BTX-B including dyspnea, respiratory compromise, weakness, and death have mostly occurred in children treated for cerebral palsy-associated spasticity. Serious systemic complications have been reported between one day and several weeks following treatment. In 2009, FDA included a Black Box WARNING that Botulinum toxin may spread from area of injection to produce symptoms consistent with botulism.

**Suggested Reading**


### Table 5.3 Side effects of the Antidepressants

<table>
<thead>
<tr>
<th>Anticholinergic</th>
<th>Antihistiminic</th>
<th>Alpha-l-blockade</th>
<th>Antidopaminergic</th>
<th>Cardiac</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry Mouth</td>
<td>Sedation</td>
<td>Orthostatic</td>
<td>Dystonia</td>
<td>Conduction</td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td>Hypotensio</td>
<td></td>
<td>Defects</td>
</tr>
<tr>
<td>Urinary Retention</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 5.2 The Antidepressants used in Pain Management

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sedating Quality</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tricyclics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>+++</td>
<td>Over 65 Y/O: 10 mg q hs,</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>+</td>
<td>increase up to 100 hsmg q hs,</td>
</tr>
<tr>
<td>Imipramine</td>
<td>+</td>
<td>hsmg q hrs, as tolerated</td>
</tr>
<tr>
<td>Desipramine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxepin</td>
<td>+++</td>
<td>Under 65 Y/O: 25 mg qhs,</td>
</tr>
<tr>
<td>Amoxapine</td>
<td>+</td>
<td>increase up to 100 mg q hs,</td>
</tr>
<tr>
<td><strong>Serotonin Specific Reuptake Inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>+/-</td>
<td>Initial dose: 20 mg (50 mg Sertraline) q AM.</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>+</td>
<td>increase to 60 mg (200 mg Sertraline) q AM as tolerated.</td>
</tr>
<tr>
<td>Sertraline</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td><strong>Atypical Antidepressants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trazadone</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Maprotiline</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>+/-</td>
<td>Initial dose: 50 mg (75 mg Venlafaxine) q AM, increase to 200mg (150 mg Venlafaxine) q AM, as tolerated</td>
</tr>
</tbody>
</table>
### Table 5.3 The Anticonvulsants used in Pain Management

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>100 mg BID, increase by 100 mg every other day up to 300 mg QID if tolerated.</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>100 mg BID, increase by 100 mg every other day up to 200 mg TID if tolerated.</td>
</tr>
<tr>
<td>Valproic Acid</td>
<td>15 mg/kg/day, increase by 5-10 mg/kg/day every other day up to 60 mg/kg/day if tolerated.</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>0.5 mg TID, increase by 0.5 mg/day every third day up to 10 mg/day if tolerated.</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>300 mg TID, increase by 300 mg every week up to 600 mg TID if tolerated</td>
</tr>
<tr>
<td>Pregablin</td>
<td>75 mg BID, increase up to 200 mg TID</td>
</tr>
</tbody>
</table>

### Table 5.4 Side effects of the Anticonvulsants

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Causative Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver Toxicity</td>
<td>All Anticonvulsants except Gabapentin</td>
</tr>
<tr>
<td>Aplastic Anemia</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Gingival Hyperplasia</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Withdrawal Seizures</td>
<td>All Anticonvulsants</td>
</tr>
</tbody>
</table>
Table 5.5 The Antiarrhythmics used in Pain Management

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route of Administration</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mexiletine</td>
<td>Oral</td>
<td>150 mg BID, increase by 150 mg every other day up to a maximum of 10 mg/kg/day divided TID if tolerated</td>
</tr>
<tr>
<td>Tocainide</td>
<td>Oral</td>
<td>400 mg TID, increase by 400 mg every other day up to 1800 mg/day</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Intravenous</td>
<td></td>
</tr>
<tr>
<td>Bretylium</td>
<td>Intravenous Regional</td>
<td></td>
</tr>
<tr>
<td>Guanethidine</td>
<td>Intravenous Regional</td>
<td></td>
</tr>
</tbody>
</table>

Table 5.6 Side effects of the antiarrhythmics

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Causative drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/Vomiting</td>
<td>All antiarrhythmics</td>
</tr>
<tr>
<td>Tremors/Irritability</td>
<td>Mexiletine</td>
</tr>
<tr>
<td>Seizures</td>
<td>Lidocaine, Mexiletine, Tocainide</td>
</tr>
</tbody>
</table>
Table 5.6  The Alpha-1 antagonists and Alpha-2 antagonists used in Pain Management

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route of Administration</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-1 antagonists</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prazosin</td>
<td>Oral</td>
<td>1 mg TID, increase by 1 mg every other day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 up to 5 mg TID.</td>
</tr>
<tr>
<td>Phenoxybenzamine</td>
<td>Oral</td>
<td>10 mg TID, increase by 10 mg every other day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Up to 40 MG</td>
</tr>
<tr>
<td>Terazosin</td>
<td>Oral</td>
<td>1 mg q Day, increase by 1 mg every other day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Up to 5 mg 1 Day.</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>Intravenous</td>
<td>0.5-1 mg/kg over 30 min. Until pain releif</td>
</tr>
<tr>
<td>Alpah-2 Agonists</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonidine</td>
<td>Oral and Transdermal</td>
<td>0.1 mg BID, increase by 0.1 mg every other</td>
</tr>
<tr>
<td></td>
<td></td>
<td>day up to 0.3 mg BID.</td>
</tr>
</tbody>
</table>

Table 5.7  Side effects of the Alpha-1 antagonists and Alpah 2 agonists

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Causative drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td>All drugs</td>
</tr>
<tr>
<td>Orthostatic</td>
<td>Prazosin, Phenoxybenzamine, Terazosine</td>
</tr>
<tr>
<td>Hypotension</td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td></td>
</tr>
<tr>
<td>CNS</td>
<td>Clonidine</td>
</tr>
<tr>
<td>Sedation</td>
<td></td>
</tr>
</tbody>
</table>
Table 5.8 Miscellaneous Drugs used in Pain Management

**Antihistamines**

Hydroxyzine 50 - 100 mg q hs

**Skeletal Muscle Relaxants**

Antispasmodics

- **Baclofen**
  
  5mg increase by 5 mg every third day up to 20 mg TID.

- **Dantrolene**
  
  25 mg q Day, increase gradually up to a maximum of 400 mg/day.

Centrally-acting agents

- **Carisoprodol** 350 mg TID
- **Chlorphenesin carbamate** 400-800 mg QID
- **Chlorzoxazone** 250-500 mg TID
- **Cyclobenzaprine hydrochloride** 10 mg TID
- **Methocarbamol** 1000-1500 mg TID
- **Orphenadrine citrate** 100 mg BID

**Antipsychotics**

Pluphenazine 1-2.5 mg QID

Haloperidol 0.5-5 mg TID

**Corticosteroids**

Methylprednisolone Individualize Dose

Dexamethasone

Prednisone

**Stimulants**

Dextroamphetamine 5-30 mg q AM

Methyphenidate 5-30 mg q AM

Caffeine 65-130 mg q AM

**Cream**

Capsaicin 0.25% or 0.75% Apply to painful area QID

EMLA cream Apply to painful area QID
PATHOPHYSIOLOGY OF PAIN

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University of California San Diego
PATHOPHYSIOLOGY OF PAIN

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The International Association for the Study of Pain defines pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage. The definition recognizes pain as a subjective experience with both psychological and sensory components. It also recognizes that tissue damage does not need to be present in order to experience pain. Pain is a symptom of an underlying illness that cannot be cured. This is consistent with over 90% of medicine in which medical doctors simply treat the symptom of illnesses without affecting the course of the underlying illness (e.g. hypertension, diabetes). It should be recognized that pain is a symptom with underlying mechanisms and neuratomic pathways. By better understanding the anatomy and physiology of pain, the practitioner can better target treatments at the underlying mechanisms.

Nociceptive pain results from activity in neural pathways caused by actual tissue damage or potentially tissue-damaging stimuli. Examples include postoperative pain, arthritis, mechanical low back pain, and sports injuries. Neuropathic pain is caused by a primary lesion or dysfunction of the nervous system. Examples include peripheral neuropathy, postherpetic neuralgia, central poststroke pain, spinal cord injury pain, and trigeminal neuralgia. Often, patients experienced a “mixed type” with both nociceptive and neuropathic components.

Mechanistically, pain can be divided into three categories: acute, facilitated and neuropathic. There is no clear boundary between these categories, and clinically there is some overlap that is often observed. Acute pain results from activation of peripheral nociceptors with thermal or mechanical stimuli that do not result in tissue injury. When the stimulus is removed, the pain ceases. Facilitated pain results when tissue injury occurs resulting in the release of chemicals that sensitize the peripheral nociceptors. There is also the central release of neuropeptides that sensitize the dorsal horn cells resulting in both a peripheral and central sensitization. A very low level of peripheral input is required to maintain the central sensitization. Neuropathic pain is pain caused by a primary lesion or dysfunction in the peripheral and/or central nervous systems.

ACUTE PAIN

Transducer receptor/ion channel complexes on peripheral nociceptor terminals respond to noxious stimuli from mechanical, chemical, or heat sources by generating depolarizing currents. If the current is sufficient, action potentials are initiated and then conducted to the CNS, where they invade central nociceptor terminals and cause the release of neurotransmitters, thus eliciting pain perception (Woolf and Salter 2000).
The functional specialization of primary sensory neurons enables, under normal circumstances, the response to low- and high-intensity peripheral stimuli to be differentiated. Low-intensity peripheral stimuli activate low-threshold receptors generating innocuous sensations, and high-intensity stimuli activate high-threshold nociceptors, which can lead to the sensation of pain. This pain is a physiologic sensation acting as a warning of potentially harmful stimuli.

**FACILITATED PAIN**

After tissue injury, there is the local release of chemicals that activate and sensitize free nerve endings. The activation results in dromic conduction into the central nervous system and antidromic conduction which results in the release of substance P from the nerve endings. The substance P degranulates mast cells and platelets to release histamine and serotonin respectively that in turn further activates the free nerve endings from which the substance P was released as well as neighboring free nerve endings. This will result in a flare response due to the vasodilatory effect of the substance P, serotonin and histamine. A-delta fibers are thought to transmit the initial sharp, easily localized, pain experienced by a person who has just been injured (first pain). C-fibers are thought to transmit the dull, poorly localized, and prolonged pain experienced after injury (second pain). A-delta fibers also act to suppress activity in C-fibers. If the C-fibers go unopposed by the A-delta fibers, the second pain is exaggerated.

**Hyperalgesia** is an exaggerated response to stimuli that activate nociceptors, both A delta and C fibers. A delta and C nociceptors are high threshold afferents in that they require a high intensity stimulus for activation. However, if they become sensitized, their threshold of activation is decreased to where a low intensity stimulus (thermal or mechanical) results in activation and the report of pain. **Primary hyperalgesia** corresponds with the injured area and the area of flare response. It is the result of lowered pain thresholds to both thermal and mechanical stimuli and involves sensitization of the peripheral nociceptor as well as sensitization of the central nervous system.

The activity in the peripheral nociceptors will also result in the release of central neuropeptides which will sensitize the dorsal horn cells. When activated, these sensitized dorsal horn cells have an exaggerated response that is perceived as much more painful than would occur in the unsensitized state. Therefore, hyperalgesia can occur through central mechanisms as well as peripheral mechanisms.

**Heat hyperalgesia** occurs within the area of primary hyperalgesia after injury as described previously. Therefore, the threshold of detecting a rise in temperature applied to the skin approaches the threshold at which the rise in temperature is painful. Clinically, this occurs in post operative pain in which the area immediately surrounding the surgical site has heat hyperalgesia. Also, in some early neuropathic pain states such as Complex Regional Pain Syndrome, the extremity is warm and erythematous and demonstrates heat hyperalgesia. This is hypothesized to be the result of “angry backfiring C-fibers” resulting in the release of substance P and degranulation of mast cells and platelets as described above. It may also be the result of a exaggerated response.
to circulating inflammatory mediators.

C-fibers enter the dorsal horn of the respective dermatome to make connections on second order neurons located in Lamina II. However, C-fibers also branch cephalad and caudal to make connections on Lamina II neurons above and below the dermatome of origination. This results in an activation of dorsal horn cells in dermatomes outside the original injury resulting in secondary hyperalgesia.

**Secondary hyperalgesia** is located in the dermatomal area outside the area of injury. The area of secondary hyperalgesia has lowered pain thresholds to mechanical but not thermal stimuli (as compared to the area of primary hyperalgesia which has lowered pain thresholds to both mechanical and thermal stimuli). Whereas the area of primary hyperalgesia involves both peripheral and central mechanisms, the area of secondary hyperalgesia involves central mechanisms only. However, a continued low level of peripheral nociceptive input is required to maintain the area of secondary hyperalgesia.

Zones of secondary hyperalgesia are measured with a punctate stimulus and involves activation of A-delta fibers that in turn activate sensitized dorsal horn cells that produce an exaggerated pain response. **Mechanical allodynia** is measured with a brushing stimulus which activates low threshold A-beta mechanoreceptors. Under normal circumstances, dorsal horn nociceptive neurons will not respond to this stimulus; however, when they become sensitized, a non painful stimulus such as a touch, brush or pressure will activate these neurons leading to pain (allodynia) (Gottschalk and Smith 1984).

**NEUROPATHIC PAIN**

Neuropathic pain (NeP) is chronic pain initiated by nervous system lesions or dysfunction and maintained by a number of mechanisms. Excess stimulation of nociceptive pathways or damage to non-nociceptive pathways alters the balance between painful and nonpainful inputs so that pain results without nociceptor stimulation.

Neuropathic pain is described by a variety of terms such as burning, shooting, or lancinating and may be present without demonstrable physical findings. NeP sensations are diverse, but three symptoms—numbness, tingling, and increased pain due to touch—appear to predominate (Backonja and Krause 2003). These symptoms illustrate the negative (sensory deficit) as well as positive (paresthesia and allodynia/hyperalgesia) phenomena that distinguish neuropathic from nociceptive pain.

Despite its clinical heterogeneity, NeP may result from a limited number of peripheral and central mechanisms that may be related to specific symptoms. For example, Gregg proposed correlations between specific neural mechanisms and four symptoms that often follow trigeminal nerve injuries, on the basis of surgical observations and animal pain models. In this paradigm, anesthesia dolorosa is associated with traumatic neuromas and central deafferentation; sympathetically mediated pain with C-fiber crosstalk in peripheral injured zones; hyperalgesia with abnormal connections...
between mechanosensitive A beta fibers and irritable central nervous system neurons; and hyperpathia with ephaptic transmission between adjacent fibers in neuromas. Although this proposal may be a simplification, it provides a useful framework for relating experimental and clinical results (Gregg 1990).

The following cellular and molecular mechanisms operating over different periods of time are thought to be involved in the abnormal peripheral and central nervous system activity associated with NeP.

1. **Ion Channels and demyelination**
   Nerve injury is reported to evoke spontaneous discharges from the cell bodies of myelinated fibers at the levels of the dorsal root ganglia, but not from the cell bodies of unmyelinated axons. The mechanism of the spontaneous activity is thought to be secondary to an increase in concentration of sodium channels in neuromas, dorsal root ganglion cells and areas of demyelination (Devor et al. 1993).

   Pain is a frequent symptom of demyelinating disease such as multiple sclerosis (Ehde et al. 2003). Normal intact nerves transmit impulses through well-insulated channels. Following nerve injury, this insulation can be disrupted, and the impulses carried in one nerve fiber may be transmitted to a neighboring fiber. Ephaptic communication or “cross-talk” has been demonstrated following stimulation of adjacent fibers in the same trunk (Devor and Wall 1990).

2. **Cytokines, enzymes and neuropeptides**
   There are also certain receptors that may accumulate that respond to cytokines and enzymes associated with inflammation. Receptors for inflammatory cytokines such as tumor necrosis factor α (TNF-α) can accumulate in injured sensory neurons and alter their function. Interleukins 1 and 6 and TNF-α are elevated in vasculitic neuropathy, chronic inflammatory demyelinating neuropathy, and noninflammatory chronic neuropathy. Cytokine levels also rise after nerve transection, and this elevation is correlated with alldynic behavior that may be linked to glutamate release and NMDA receptor activation (Liu and al. 2002).

   Membrane-type 5 matrix metalloproteinase (MT5-MMP) has been implicated in injury-associated spinal cord remodeling and development of NeP. Sciatic nerve damage results in sprouting of A beta afferents from laminae III–VI and into lamina I of the dorsal horn and in the development of mechanical allodynia (see discussion below). Neither sprouting nor allodynia occurs after nerve damage in mice lacking the gene for MT5-MMP (Komori et al. 2004).

   Nerve injuries associated with the development of NeP alter the expression of neuropeptides and their receptors. Vanilloid receptor 1 (VR1) is expressed on peripheral terminals of A delta and C fibers. However, in rats with streptozotocin-induced diabetes, peripheral terminals of A beta fibers also express VR1. Substance P (SP) is normally released from the central terminals of A delta and C fibers to bind with neurokinin-1 (NK-1) receptors on nociceptive neurons in the dorsal horn. NK-1 mRNA expression in
the mouse lumbar dorsal horn is increased after partial sciatic nerve ligation, and this rise is correlated with thermal hyperalgesia. These results have prompted the suggestion that nerve injury results in synthesis and tonic release of SP by A beta fibers, which initiates ongoing excitation of NK-1–expressing spinal nociceptive neurons (Rashid et al. 2003).

3. **A beta Sprouting**

Peripheral nerve injury triggers central sprouting of myelinated afferents. The myelinated afferents located in deeper layers of the dorsal horn cells (laminae III and IV) sprouting superficially to reach superficial layers of the dorsal horn (laminae I and II). Therefore, tactile nonpainful stimuli that activate large myelinated afferents will in turn activate superficial layers of the dorsal horn in turn activating spinothalamic tract neurons which will result in a painful state (alldynia) (Woolf and al. 1992).

4. **Sympathetic-Somatosensory Crosstalk**

Discharge of afferent fibers has been observed following stimulation of sympathetic nerve fibers in the same nerve trunk. Sympathetic communication with afferent neurons is hypothesized to be the result of an increase in alpha adrenergic receptors in damaged primary afferent axons. Crosstalk between sympathetic and somatosensory afferents can develop in neuromas and dorsal root ganglions (DRG).

**Note:** please define DRG. Sympathetic axons are present in neuromas, and α-adrenoceptor–mediated excitatory coupling has been demonstrated in both neuromas and DRGs (Devor and al. 1981).

In addition to alterations in adrenergic receptor expression, a recent report indicated that nerve injury causes sprouting of sympathetic fibers that invade the DRG to form functional synapses. These sprouting fibers contain catecholamines, and it has been demonstrated that ectopic discharges may originate at the DRG by direct innervation from these sympathetic fibers that form basket like structures around large diameter cell bodies of the DRG (McLachlap and al. 1993).

5. **GABA Down-regulation**

Spinal inhibitory interneurons modulate the peripheral-to-central transmission of pain signals, thus “gating” ascending sensory information. γ-Aminobutyric acid (GABA) and glycine and their receptors are abundant in the superficial dorsal horn, but their levels are regulated by primary afferent input and change significantly after nerve injury. Sciatic nerve transection decreases the number of GABA-immunoreactive cells in dorsal horn laminae I–III, and this may “open the gate” to allow more excitatory signals from pain (or nonpain) pathways to reach the brain. Nerve damage also reduces expression of GABA\textsubscript{A} receptor \(\alpha_2\) subunit mRNA in DRG cells, and this may disrupt the normal presynaptic inhibition that modulates neurotransmitter release by these cells (Polgar et al. 2003).

6. **Glutamatergic Neurotransmission**

Increased glutamatergic neurotransmission may also contribute to hyperexcitability and NeP. Repeated noxious stimulation leads to temporal summation of dorsal horn excitatory postsynaptic depolarizations, and this amplification is reduced by the n-methyl-d-aspartate (NMDA) **Note:** please define NMDA receptor antagonist d-2-
amino-5-phosphonovaleric acid (d-APV), suggesting mediation by an increase in glutamate release from primary afferents and subsequent binding to NMDA receptors. Intrathecal NMDA causes an increase in spontaneous activity of dorsal horn neurons that can be reversed by d-APV. Persistent inflammation that gives rise to hyperalgesia is also associated with up-regulation of metabotropic glutamate receptors in the dorsal horn.

Dorsal horn neurons express amino-3-hydroxy-5-methylisoxazol propionic acid (AMPA)/kainate-type glutamate receptors; these non-NMDA receptors are thought to be primarily involved in detecting and responding to innocuous stimuli, but AMPA/kainate-NMDA receptor interactions are involved in C-fiber wind-up and long-term potentiation in dorsal horn neurons.

Glutamatergic transmission is potentiated by neuropeptides. For example, thyrotropin-releasing hormone has a slow priming effect that enhances NMDA receptor–mediated nociceptive transmission in the dorsal horn. Peripheral interactions between NK1 and NMDA receptors may also potentiate pain. NK1 receptor activation is thought to potentiate glutamatergic transmission in the spinal cord via NMDA-independent mechanisms.

Protein kinase C (PKC) potentiates NMDA currents by reducing the magnesium block and increasing the probability of channel openings. An additional consequence of protein phosphorylation is tolerance to opioids, which may result from desensitization of the opioid receptor by G-protein kinase 3.

Glutamatergic neurotransmission, most notably that involving NMDA receptors, also results in significant damage-associated changes in the anatomy of the spinal cord. For example, sciatic nerve transection results in degeneration of spinal dorsal horn neurons, and this apoptosis can be prevented when the NMDA antagonist MK-801 is injected before transection and then continuously infused.

Nociceptive processing also involves the expression of immediate early genes, a process partially regulated by glutamate receptors. Activity-dependent stimulation of kinases such as extracellular signal-regulated protein kinase), the Ras cascade, and other transcriptional factors appears to be involved in inflammatory pain and NeP (Kristensen and Gordh 1997).
REFERENCES:

POSTOPERATIVE PAIN MANAGEMENT

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Assistant Clinical Professor of Anesthesiology

Introduction

Acute on Chronic Post-Operative Pain
UCSD Post-operative Pain Algorithms
Pre-Emptive Analgesia
Patient Controlled Analgesia
Opioids, Adjuvant Analgesics and Conversion
Inpatient Ketamine Infusion
Epidural Analgesia
Spinal Analgesia

Introduction

Acute pain is defined as pain that arises from tissue injury that is expected to resolve once the patient recovers from the injury. The most common type of acute pain is postoperative pain. Although we have many effective modalities for the treatment of postoperative pain, many patients suffer needlessly from under-treatment of their pain postoperatively.

Pain is more difficult to control if not adequately treated and allowed to become severe. Patients have a great deal of anxiety about the management of their acute pain. Higher levels of anxiety will increase distress and the psychological experience of the painful stimuli. Addressing their concerns will go a long way towards alleviating this anxiety and thus improving their pain control.

All medications and methods of providing post-operative pain management have potential and expected adverse effects. Opioid medications are the gold standard for post-operative pain management but have side effects that run the spectrum from annoying, such as pruritis and nausea, to potentially fatal respiratory depression. There is no ceiling effect on the analgesia from opioids; however adverse effects will limit the total dose tolerated. Multimodal analgesia in the post-operative setting offers the promise reducing pain by using multiple agents that work on different receptors or at different levels of the pain processing pathway. In this way the total dose of opioid medications may be reduced in order to limit adverse effects.

In order to limit adverse effects and patient confusion, the preferred pain regimen is one that is: 1) simple, 2) at the lowest acceptable doses, 3) delivered by the oral route. Simplicity dictates that only one short-acting opioid be used at a time with or without one long-acting opioid. In the transition period from IV to PO it may be appropriate to have
an IV agent for rescue analgesia in conjunction with a short-acting PO opioid but with clear instructions to patient and nurse about when to choose one over the other.

**Acute on Chronic Post-Operative Pain**

Pain after surgery is the primary concern of patients who are surveyed prior to elective surgical procedures [1, 2]. This ranks as a higher concern than even the success of the surgical procedure. When surveyed after discharge from the hospital, the majority of post-surgical patients report mild to moderate pain. However, up to one-third of patients report severe pain after elective surgery [1, 2]. Patients with a history of chronic pain pose a particular challenge and are at high risk of having difficult-to-control postoperative pain.

Chronic pain months after surgery is seen after a variety of different surgical procedures. The highest rates of chronic post-surgical pain occur after limb amputations, thoracotomy, and mastectomy [3, 4, 5]. There are several risk factors that are associated with severe acute post-operative pain and the development of chronic postoperative pain [3, 4, 5]:

1) Age  
2) Gender  
3) Pre-operative Anxiety  
4) Catastrophizing  
5) Co-morbid chronic pain conditions  
6) Severity of Acute Post-op Pain  
7) Pre-operative opioid use  
8) Surgical Factors  
9) Anesthetic Factors

Patients with chronic pain and on high dose opioid therapy (>100-200mg oral morphine equivalent) should have a preoperative pain consult to discuss options for pain management and develop a post-operative pain plan. Options for perioperative pain control include:

1) pre-emptive analgesia  
2) intravenous patient controlled analgesia  
3) intermittent oral, IV, or IM analgesics and adjuvants  
4) epidural, intrathecal, or regional analgesia  
5) intravenous ketamine infusion

If the patient has preexisting pain, special attention should be given to the current medications, as some will affect the postoperative treatment of pain. If the patient is on an NSAID, it should be stopped at least 24 hours prior to surgery. Aspirin should be stopped 7 days prior to surgery. The COX-2 inhibitors do not inhibit platelet aggregation like non-selective COX inhibitors and thus do not need to be discontinued. If the patient is taking an opioid, the patient may benefit from weaning the opioid to reverse the tolerance although the evidence for this effect is lacking. Patients should be instructed to take their regular opioid medication the morning of surgery and the surgical service
should be instructed to restart the patient’s regular long-acting agent immediately post-op with PCA or other short-acting agent to treat the acute post-surgical pain.

UCSD Post-Operative Pain Algorithm’s

TABLE 1

ADULT MAJOR SURGERY
(Intravenous Patient Controlled Analgesia)*

<table>
<thead>
<tr>
<th>Pain Persisting or Increasing</th>
<th>Pain Persisting or Increasing</th>
<th>Pain Persisting or Increasing</th>
<th>Pain Persisting or Increasing</th>
</tr>
</thead>
<tbody>
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<td>IV PCA Morphine</td>
<td>Anxiety?</td>
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Pre-emptive Analgesia

The tissue injury that occurs during surgery results in a barrage of noxious stimuli transmitted from the periphery to the central nervous system throughout the surgery and continuing into the post-operative period. This high threshold noxious input to the PNS and CNS results in a prolonged excitability known as “hypersensitivity” [6, 7].

Post-surgical pain is an inflammatory pain state due to tissue injury and the subsequent release of inflammatory mediators. These mediators form a “sensitizing soup” of cytokines, neuropeptides, prostaglandins, hydrogen ions, norepinephrine, bradykinin, histamine, and other neuroactive substances. This results in sensitization of peripheral nociceptors lowering their threshold for transduction. At the same time noxious input to dorsal horn neurons from repeated high-threshold C-fiber input causes post-synaptic central sensitization. The response of the dorsal horn neurons to a given stimulus is increased in intensity and duration (hyperalgesia). These same neurons receive input from A-beta fibers. When the post-synaptic NMDA receptors have been flooded with Glutamate from C-fiber input, stimulation of the low threshold A-beta fibers can activate the pain pathways (allodynia).

Pre-administration of NMDA receptor antagonists such as ketamine has been shown to inhibit the development of opioid tolerance. However, once tolerance is
expressed, it is not reversed by these agents [8]. The NMDA receptor antagonist effect has also been shown to reduce post-operative opioid requirements and pain scores [9, 10, 11]. The usual protocol for ketamine administration for pre-emptive analgesia is a pre-incision bolus of 0.3-0.5 mg/kg followed by a low-dose infusion of 5-10 mcg/kg/min. The infusion should be stopped about 45 minutes before the end of surgery to limit delay in emergence and emergence delirium.

While NMDA antagonism works post-synaptically to limit central sensitization calcium channel modulators work pre-synaptically in the CNS. Gabapentin and pregabalin have been studied as a pre-operative dose one hour before surgery with or without post-operative continued doses. The majority of studies have shown decreased opioid requirements and decreased post-operative pain scores. One study looked at pain 6 months after surgery and found a significant reduction in chronic pain compared to placebo. The protocols for gabapentin have varied from one study to the next but the majority used a pre-operative dose of 1200 mg. One study compared a single pre-operative dose of 300mg, 600mg, 900mg or 1200mg compared to placebo and found significant pain score reduction vs. placebo at 600mg and above but no difference between 600 900 or 1200mg [9, 12]. The most commonly used dose of pregabalin was 150mg 1-2 hours before surgery [13].

Use of regional or neuraxial anesthesia to limit the input of noxious stimuli to the dorsal horn has also been shown to reduce post-operative opioid requirements and pain scores. When the planned surgical procedure and surgeon is amenable to regional nerve block or neuraxial anesthesia these techniques should be strongly considered. This is especially true for patients with multiple risk factors for difficult-to-control post-operative pain.

**Intravenous Patient Controlled Analgesia (PCA)**

Since the use of patient-controlled analgesia began in the early 1970’s it has become a well-accepted standard for post-operative pain control. The concept behind use of PCA is simple. That administration of small bolus doses by the patient with a temporal lockout and hourly maximum dose will provide better analgesia in a more timely fashion than nurse administered prn bolus doses.

Numerous randomized controlled trials have compared PCA to a standard prn nurse administered bolus regimen. In 2006 a Cochrane review of these studies found a small but significant analgesic benefit for PCA and better patient satisfaction [14]. The PCA groups consumed more opioid than the prn analgesia groups and had slightly more pruritis but no increased incidence of other opioid-induced adverse reactions.

A multicenter retrospective review of 254 patients post hip and knee arthroplasty comparing PCA morphine, hydromorphone, and fentanyl showed a significant difference in opioid induced adverse reaction (OIAR) [15]. The OIAR includes nausea, vomiting, pruritis, sedation, constipation, respiratory depression, hallucinations, urinary retention, confusion, agitation and monoclonus. After controlling for equianalgesic dose the fentanyl group had significantly lower incidence of OIAR (20%) compared to morphine
(48%) or hydromorphone (46%). The breakdown of adverse reactions is below. A secondary analysis of pain scores showed significantly lower pain scores in the fentanyl group vs. either morphine or hydromorphone. However the fentanyl group had proportionally more hip and fewer knee surgery patients compared to morphine and hydromorphone groups, which would skew pain scores. While not statistically significant in this study the OIAR trended lower for hydromorphone compared to morphine for pruritis, urinary retention, headache and confusion. There is no well done study that shows a clear analgesic benefit of one agent over another. From a pharmacokinetic basis it would make sense that a fentanyl PCA bolus would act slightly more rapidly than either morphine or hydromorphone but the analgesic effect would be shorter in duration.

TABLE 3: Percent of patients with various adverse reactions using PCA morphine vs. hydromorphone vs. fentanyl

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Morphine</th>
<th>Hydromorphone</th>
<th>Fentanyl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/Vomiting</td>
<td>31</td>
<td>33</td>
<td>18</td>
</tr>
<tr>
<td>Pruritis</td>
<td>16</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Urinary Retention</td>
<td>16</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Sedation</td>
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<td>1</td>
</tr>
<tr>
<td>Respir Depression</td>
<td>8</td>
<td>7</td>
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<tr>
<td>Headache</td>
<td>7</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Confusion</td>
<td>5</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

In converting from PCA to oral first determine the prior 24 hour usage. If the pain is expected to be of short duration, the patient was not on long-acting opioids before surgery, and the 24 hour usage was low then conversion to prn short acting opioids may be the most prudent. If the patient will likely have an extended recovery and the 24 hour usage was relatively high then convert to long-acting opioid with short acting for breakthrough. Approximately 2/3 of the total should be long-acting and 1/3 as short-acting. If the patient is remaining in the hospital after conversion to oral then a prn IV opioid for severe rescue analgesia may be reasonable.

TABLE 4 UCSD IV PCA Guidelines

<table>
<thead>
<tr>
<th>Opioid Nontolerant Patient</th>
<th>Morphine</th>
<th>Hydromorphone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cont. Inf*</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Dose</td>
<td>1 mg</td>
<td>0.2 mg</td>
</tr>
<tr>
<td>Lockout</td>
<td>10 minutes</td>
<td>10 minutes</td>
</tr>
<tr>
<td>Nurse Administered Bolus</td>
<td>3 times the patient activated dose q 2-4 hours</td>
<td>3 times the patient activated dose q 2-4 hours</td>
</tr>
<tr>
<td>No Relief Dose</td>
<td>Increase by 0.5mg increments up to 3 mg</td>
<td>Increase by 0.1 mg increments up to 0.6mg</td>
</tr>
</tbody>
</table>
Opioid Tolerant Patient

<table>
<thead>
<tr>
<th></th>
<th>Morphine</th>
<th>Hydromorphone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cont. Inf*</td>
<td>0.5 – 1.0 mg</td>
<td>0.1 – 0.2 mg</td>
</tr>
<tr>
<td>Dose</td>
<td>1.5 mg</td>
<td>0.4 mg</td>
</tr>
<tr>
<td>Lockout</td>
<td>10 minutes</td>
<td>10 minutes</td>
</tr>
<tr>
<td>Clin. Activ. Dose</td>
<td>3 times the patient activated dose q 2-4 hours</td>
<td>3 times the patient activated dose q 2-4 hours</td>
</tr>
<tr>
<td>No Relief Dose</td>
<td>Increase by 1.0mg increments up to 5 mg</td>
<td>Increase by 0.2 mg increments up to 1.0mg</td>
</tr>
</tbody>
</table>

* Use with caution only in opioid tolerant patients. Requires monitored setting with continuous pulse-oxymetry and/or continuous ETCO2 monitoring.

Intermittent IV/PO Opioids, Non-opioids, and Adjuvant Analgesics

The majority of patients with mild to moderate post-operative pain will do well with intermittent dosing of IV and/or PO analgesics. Opioids, acetaminophen and to a lesser extent NSAIDS are the mainstay of post-operative analgesia. The choice of opioid and dosing will depend on the severity of post-op pain but the majority of short-acting oral opioids will require dosing every 4-6 hours. Patients who are on sustained release or long-acting opioids chronically prior to surgery should have these restarted post-operatively. They will need additional short-acting agents to cover the additional pain of the surgical procedure. For those patients who are using larger amounts of short-acting agents in the post-operative period and are expected to need opioids for several weeks after surgery the addition of a sustained release opioid may be appropriate. The prescribing information for the fentanyl patch lists post-operative pain as a contraindication for use of the patch. Due to the complex pharmacokinetics, difficulty with titration and delayed respiratory depression methadone is not an optimal choice for post-operative pain.

Using a combination of opioid and non-opioid agents may improve analgesia while reducing opioid doses, and thus adverse effects, from use of a single agent. Acetaminophen and NSAIDS are commonly used non-opioid agents. For patients who are NPO Toradol (ketorolac) or Ofirmev (acetaminophen) are non-opioid options. Patients who are experiencing painful muscle spasm may benefit from the addition of a muscle relaxant such as cyclobenzaprine, diazepam, or tizanidine either prn or scheduled. Anxiety combined with post-operative pain will increase distress and the experience of pain will be heightened. The use of a benzodiazepine may help manage anxiety and distress as well as muscle spasm.

Topical agents, such a Lidoderm patch, have been used as adjuvants when there is a discrete area of pain or for co-occurring low back pain in post-surgical patients on bed
rest. In a double blind placebo controlled study of men undergoing radical retropubic prostatectomy the lidoderm patch was cut in half and placed on either side of the incision. The patch was left in place for 24 hours then removed with dressings. There was no difference in morphine consumption but a significant decrease in pain with coughing for 24 hours and pain at rest for 6 hours post-operatively [16].

Antiepileptic drugs that act by modulating calcium channels (gabapentin and pregabalin) are increasingly being used for post-operative pain. These agents have an opioid sparing effect and may limit the development of tolerance to opioids. In addition they modulate the input of noxious stimuli to dorsal horn neurons and may inhibit the development of central sensitization even when given post-operatively. Choice of agent depends mostly on economic practicality and speed of titration. If the agent will be continued upon discharge and insurance coverage is an issue gabapentin will be the preferred agent. However, pregabalin can usually be started at 75mg bid and titrated in 1-2 days to a therapeutic dose of 150mg bid. Gabapentin may take longer to titrate to an effective dose of 600-900mg q8 hours.

### TABLE 5: Opioid Conversion

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<thead>
<tr>
<th>Opioid</th>
<th>Oral Dose (mg)</th>
<th>Intravenous Dose (mg)</th>
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<tbody>
<tr>
<td>Morphine</td>
<td>30</td>
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<tr>
<td>Codeine</td>
<td>200</td>
<td>130</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>30</td>
<td>-</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Meperidine</td>
<td>300</td>
<td>75</td>
</tr>
<tr>
<td>Methadone*</td>
<td>10*</td>
<td>7.5 - 10</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>20</td>
<td>-</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>-</td>
<td>100 micrograms</td>
</tr>
<tr>
<td>Transdermal Fentanyl</td>
<td>Transdermal fentanyl</td>
<td></td>
</tr>
<tr>
<td></td>
<td>60-120mg = 25mcg patch</td>
<td></td>
</tr>
<tr>
<td></td>
<td>120-220mg = 50mcg patch</td>
<td></td>
</tr>
<tr>
<td></td>
<td>220-300mg = 75mcg patch</td>
<td></td>
</tr>
<tr>
<td></td>
<td>300-400mg = 100mcg patch</td>
<td></td>
</tr>
</tbody>
</table>

*Methadone conversion is non-linear and dose dependent. Respiratory depression may be delayed and requires slow titration. Above is rough guide for low dose morphine-to-methadone conversion (<100mg/day oral morphine). With higher doses of morphine the conversion ratio becomes increasingly conservative. Methadone is approximately 80% bioavailable. Methadone-to-morphine conversion at all doses is x3.*
TABLE 6: Morphine to Methadone Conversion

<table>
<thead>
<tr>
<th>Daily Oral Morphine Dose</th>
<th>Morphine : Methadone Conversion Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100mg/day</td>
<td>3:1</td>
</tr>
<tr>
<td>100-300mg/day</td>
<td>5:1</td>
</tr>
<tr>
<td>300-600mg/day</td>
<td>10:1</td>
</tr>
<tr>
<td>600-800mg/day</td>
<td>12:1</td>
</tr>
</tbody>
</table>

Skeletal Muscle Relaxant Guidelines
Antispasmodics
- Baclofen: Start 5 mg PO TID, increase every 3 days up to 20mg TID
- Tizanidine: 4-8 mg PO TID/QID, up to 36mg/day

Centrally Acting Agents
- Carisoprodol: 350 mg PO TID/QID
- Cyclobenzaprine: 10 mg PO TID, up to 60mg/day
- Diazepam: 2-10 mg IV or PO BID-QID
- Metaxalone: 800mg PO TID/QID
- Methocarbamol: 750-1500mg PO TID/QID

Inpatient Ketamine Infusion
Ketamine is a dissociative anesthetic that has analgesic properties at subanesthetic doses. Its potent NMDA antagonism is the primary mechanism of analgesic action. It also has interactions with calcium and sodium channels as well as noradrenergic and serotonergic reuptake, which may contribute to analgesic effect. In the setting of chronic pain, low dose ketamine infusions have been shown to reduce phantom limb pain, neuropathic pain, fibromyalgia pain and ischemic limb pain. It has also been shown to reduce cancer related pain especially when there is a neuropathic component [17].

The common side effects are sedation, increased GI secretions, dysphoria and hallucinations. Co-administration of IV benzodiazepines (lorazepam 0.5mg IV q4) and glycopyrrolate can ameliorate some of these adverse effects. Relative contraindications are unstable cardiovascular disease, intraocular hypertension, active psychosis, recent CVA or increased ICP.

The therapeutic dose range is large. Given the lack of significant respiratory depression the risk of overdose is also low. Most of the institutions using ketamine infusions for analgesia, as opposed to sedation, have a starting dose of 0.2mg/kg/hr up to a maximum of 0.5mg/kg/hr. This is compared to an anesthetic dose range of 1-5 mg/kg/hr as a sole agent. The UCSD protocol for use of ketamine analgesia outside of the operating room requires the orders be written by a member of the Inpatient Pain Service or the Howell Palliative Care Service in close coordination with the patient’s primary service. This may be done in the Thornton ICU or Thornton IMU (2 east). All patients
will have continuous ETCO2 monitoring in place. The infusion will be a continuous basal with no patient controlled bolus or nursing administered bolus allowed.

**Neuraxial Analgesia**

**Anticoagulation Guidelines**

The American Society of Regional Anesthesia (ASRA) has published guidelines regarding the use of anticoagulant and antiplatelet agents prior to neuraxial needle placement and during use of neuraxial indwelling catheters [18]. This summary is from the third edition published January 2010. Also included are two newer agents not mentioned in the ASRA guidelines (Pradaxa and Effient).

Tryba [19] identified 13 cases of spinal hematoma after 850,000 epidural anesthetics and 7 cases among 650,000 spinal techniques. Using these observations, the calculated incidence has been estimated to be less than 1 in 150,000 epidural and less than 1 in 220,000 spinal anesthetics [20]. However, the series involved in these calculations were conducted before the implementation of routine perioperative thromboprophylaxis.

A more recent in-depth analysis of the claims related to nerve injury after regional anesthesia between 1980 and 1999 reported 36 spinal hematomas associated mainly with vascular or orthopedic surgical procedures. Three-fourths of patients had evidence of a preexisting or iatrogenic coagulation abnormality [21]. Over half the patients received intravenous heparin during a vascular surgical or diagnostic procedure, often in combination with other medications that impair coagulation. Consistent with The presenting symptom was more often increased motor block (83% of cases) rather than back pain (25% of cases). Importantly, the presence of postoperative numbness or weakness was typically attributed to local anesthetic effect rather than spinal cord ischemia, which delayed the diagnosis. Although the symptoms were noted typically on the first postoperative day, often 24 hrs or more elapsed before diagnosis. There were permanent deficits in 90% of patients.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Needle/Catheter Placement</th>
<th>Catheter Removal</th>
<th>Start/restart After Placement/Removal</th>
<th>Indwelling Neuraxial Catheters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin SQ 5000 q12 hrs</td>
<td>1 hour before first/next dose</td>
<td>1 hour before next dose</td>
<td>1 hr</td>
<td>OK</td>
</tr>
<tr>
<td>Heparin SQ 5000 q8 hours or &gt;10,000 units/day</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Heparin IV infusion</td>
<td>Discontinue 4 hrs and check PTT normalized</td>
<td>NR</td>
<td>1 hour</td>
<td>NR</td>
</tr>
<tr>
<td>Intra-op Vascular surgery heparinization</td>
<td>1 hour before heparin</td>
<td>2-4 hours after last heparin dose</td>
<td>1 hour</td>
<td>OK</td>
</tr>
<tr>
<td>Enoxaparin 40mg SQ qDay</td>
<td>Wait 10-12 hrs after last dose</td>
<td>Wait 10-12 hours after last dose</td>
<td>2 hours</td>
<td>OK</td>
</tr>
<tr>
<td>Enoxaparin (Lovenox) 30mg SQ BID</td>
<td>Wait 24 hours after last dose</td>
<td>NR – remove before first dose</td>
<td>2 hours</td>
<td>NR</td>
</tr>
<tr>
<td>Enoxaparin treatment dose (1mg/kg/bid or 1.5 mg/kg/day)</td>
<td>Wait 24 hrs after last dose</td>
<td>NR – remove before first dose</td>
<td>2 hours</td>
<td>NR</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Hold 5 days and check INR &lt;1.3</td>
<td>INR &lt;1.5</td>
<td>Same day</td>
<td>Daily INR and remove when INR &lt;1.5</td>
</tr>
<tr>
<td>NSAIDS/Aspirin</td>
<td>OK</td>
<td>OK</td>
<td>--</td>
<td>OK</td>
</tr>
<tr>
<td>Clopidogrel (Plavix)</td>
<td>Hold 7 days</td>
<td>NR</td>
<td>Same day</td>
<td>NR</td>
</tr>
<tr>
<td>Ticlopidine (Ticlid)</td>
<td>Hold 14 days</td>
<td>NR</td>
<td>Same day</td>
<td>NR</td>
</tr>
<tr>
<td>Dabigatran (Pradaxa)</td>
<td>Hold 7 days</td>
<td>NR</td>
<td>Same day</td>
<td>NR</td>
</tr>
<tr>
<td>Prasugrel (Effient)</td>
<td>Hold 7 days</td>
<td>NR</td>
<td>Same day</td>
<td>NR</td>
</tr>
<tr>
<td>abciximab, (Repro)</td>
<td>Discontinue 48 hours</td>
<td>NR</td>
<td>“Contraindicated within 4 weeks of surgery”</td>
<td>NR</td>
</tr>
<tr>
<td>eptifibatide, and tirofiban (Integrallin and Aggrastat)</td>
<td>Discontinue 8 hours</td>
<td>NR</td>
<td>“Contraindicated within 4 weeks of surgery”</td>
<td>NR</td>
</tr>
</tbody>
</table>
Heparin: a pentasaccharide that binds to antithrombin (AT) III and accelerates its ability to inactivate thrombin (factor IIa), factor Xa, and factor IXa.

Low Molecular Weight Heparin: binds to and accelerates the activity of antithrombin III. Same MOA as heparin but more anti Xa activity than anti IIa.

Warfarin: interferes with the synthesis of the vitamin K-dependent clotting factors, factor II (thrombin), VII, IX, and X. In patients with INR greater than 1.5 but less than 3, removal of indwelling catheters should be done with caution and the medication record reviewed for other medications that may influence hemostasis that may not effect the INR (eg, NSAIDs, ASA, clopidogrel, ticlopidine, UFH, LMWH). Neurologic status should be assessed before catheter removal and continued until the INR has stabilized at the desired prophylaxis level. In patients with an INR greater than 3, the warfarin dose should be held or reduced in patients with indwelling neuraxial catheters.

NSAIDS/Aspirin: inhibit platelet cyclooxygenase and prevent the synthesis of thromboxane A2. COX-2 is an inducible enzyme that is not expressed in platelets and thus does not cause platelet dysfunction. After single and multidosing, there have not been findings of significant disruption of platelet aggregation, and there is no history of undesirable bleeding events. Use in combination with other antiplatelet or antithrombotic agents may increase bleeding risk. ASRA guidelines recommend against use of NSAIDS/ASA with LMWH or heparin prophylaxis and indwelling epidural catheters.


Abciximab, eptifibatide, and tirofiban: platelet GP IIb/IIIa receptor antagonists. Inhibit platelet aggregation by interfering with platelet-fibrinogen and platelet-von Willebrand factor binding.

Dabigatran (Pradaxa): specifically and reversibly inhibits both free and clot-bound thrombin.

Prasugrel (Effient): irreversibly binds platelet adenosine diphosphate receptors inhibiting activation and decreasing aggregation. Thienopyridine derivative in the same class as clopidogrel.

Local Anesthetic Systemic Toxicity (LAST)

ASRA recommendations for minimizing, recognizing and treating LAST [21]:

- Use lowest effective dose
- Aspirate prior to each injection
- Inject in incremental aliquots 3-5 ml each with a 30 second pause in between
- Epinephrine to identify IV injection: >10 bpm or >15 mmHg increase in HR/SPB
- Progressive Signs of LAST:
  - Initial CNS signs: agitation, auditory changes, metallic taste
  - Progressing to: seizures, CNS depression, respiratory arrest
  - Then Cardiovascular Toxicity: Hypertension, tachycardia, ventricular arrhythmias
  - Culminating in: bradycardia, conduction block, asystole
Phases may not occur linearly but simultaneously or present immediately with cardiovascular collapse

- Timing: often <60 seconds if intravascular injection but may be delayed up to 15 minutes if in extremity or due to tissue absorption
- Presentation is atypical in timing or progressive symptom presentation in up to 40% of cases
- Treatment for LAST
  - Airway management
  - Seizures: IV Benzodiazepine
  - Cardiac Arrest: ACLS; epinephrine in small initial bolus doses; amiodarone is preferred for arrhythmias; 1.5 ml/kg 20% lipid emulsion bolus followed by 0.25 ml/kg/min infusion for 10 minutes after cardiac stability achieved; re-bolus and increase infusion to 0.5 ml/kg/min if stability not achieved; 10 ml/kg over 20 min is max recommended dose; propofol is NOT a substitute for 20% lipid emulsion

Intrathecal

Intrathecal (IT) drug administration can occur anywhere along the axis depending on where the therapeutic effect is needed. However, because the spinal cord ends at the L1-2 level, it is more common to use the lumbar approach. Because of the continuity of the IT space along the spine axis, the location of the drug delivery becomes less important than does epidural drug delivery. Therefore, the lumbar delivery of analgesic agents has been studied in a variety of surgical procedures. This section will review the various agents used for different surgical procedures. Whereas regional anesthesia has been demonstrated to blunt the stress response after lower abdominal and orthopedic surgery, this has not been demonstrated in thoracic and upper abdominal surgery. Therefore it is important to review the effects of spinal drug delivery for postoperative pain control on different surgical procedures.

Morphine

With the discovery that the direct application of opioids to the spine resulted in intense analgesia, the clinical use of spinal morphine for postoperative pain soon followed [23]. By far, morphine has been the most extensively used and studied for postoperative pain relief in a wide variety of patients. Since morphine has the lowest lipid solubility of all the opioids, it theoretically will have the widest segmental spread after intrathecal delivery. Indeed this has been demonstrated since the lumbar intrathecal delivery of morphine has been shown to provide postoperative pain relief in surgical procedures involving both lumbar and high thoracic dermatomes.

Thoracotomy – There are several studies evaluating the efficacy of intrathecal morphine (ITM) for pain after thoracotomy. Nordberg et al demonstrated a variable but long-lasting analgesia after ITM doses of 0.25-0.5 mg. Compared to the epidural delivery, the onset of analgesia was delayed for the IT delivery. However, the mean duration of analgesia was dose dependent and comparable between the IT and epidural delivery (8.6-15.6 hours)[24]. The difference in onset is likely due to the systemic absorption of the epidural morphine resulting in early pain relief as compared to the time is takes the
morphine to diffuse up the axis to reach thoracic spinal cord receptors after intrathecal delivery. The similarity in duration between the two methods is explained by similar diffusion kinetics of the two techniques in the intrathecal space. In another study, Gray et al demonstrated that the IT delivery of morphine (10 mcg/ml) mixed with normal saline resulted in a longer duration of pain relief after thoracotomy than when mixed in dextrose[25]. Distribution of hyperbaric agents (mixed in dextrose) is governed by patient position whereas patient position has no influence over isobaric solution (mixed in normal saline). In another study, Neustein et al administered 12mcg/kg of ITM for postthoracotomy pain. They demonstrated a significantly less utilization of systemic meperidine for more than 24 hours as compared to controls [26].

**Upper Abdominal Surgery** – Downing et al demonstrated that 0.8 mg of ITM significantly reduced the need for intravenous papaveretum after cholecystectomy for up to 48 hours as compared to controls. The analgesic requirements were similar between the two groups by 72 hours [27]. In a similar study on patients undergoing upper abdominal surgery, patients received on average 28 hours of pain relief after 0.5mg ITM [28]. In an attempt to determine the optimum ITM dose for postoperative pain relief, Yamaguchi et al performed a dose response study in cholecystectomy patients using doses ranging from 0.0 to 0.2 mg. They showed that pain relief was greatest with doses of 0.06 mg and above; however, respiratory depression occurred with doses of 0.15 mg and above. They concluded that the optimum dose for cholecystectomy was between 0.06-0.12mg [29]. Most recently, Motamed et al demonstrated significantly lower analgesic requirements after 0.075 – 0.1 mg ITM as compared to control in patients undergoing cholecystectomy [30].

**Cardiac Surgery** – Much attention has been focused on the use of intraspinal opioids for the treatment of post cardiac surgery. Potential advantages of this technique are quicker recovery and thus lessened time between completion of the surgery and extubation. Fitzpatrick et al studied the effects of 1 or 2 mg ITM compared to intravenous morphine. They concluded that both doses produced significantly better analgesia than IV morphine but that the 2 mg ITM dose resulted in more respiratory depression [31]. In a placebo controlled study, Vanstrum et al demonstrated that 0.5 mg of ITM resulted in significantly less intravenous morphine in the first 30 hours after surgery [32]. The ITM group also required significantly less sodium nitroprusside in the first 24 hours. Side effects were similar between groups. Using higher doses, Aun et al compared the effects of 2 and 4 mg of ITM with controls. The ITM patients had less pain and sedation as compared to controls. However, all patients were electively intubated and therefore respiratory depression could not be assessed [33]. The effects of ITM on early extubation has no effect with doses ranging from 8-10 mcg/kg [34-36].

**Lower abdominal surgery** – There are several studies evaluating the effects of ITM on the pain of adult urologic surgery using doses ranging from 0.1 – 1 mg. All doses resulted in analgesia that was significantly better than placebo with a dose response effect. However, there also appears to be increasing side effects with increasing dose [37-41]. In gynecologic surgery, doses ranging from 0.1-0.5 mg ITM have been studied. All doses resulted in superior analgesia over control but again side effects are dose
dependent. The optimum dose for gynecologic surgery appears to be about 0.3 mg [42, 43]. Finally, Amanor-Boad et al demonstrated that 0.5 mg ITM resulted in better analgesia compared to control for up to 8 hours after hemmorhoidectomy [44].

**Orthopedic surgery** – The effects of ITM on postoperative pain has been the most extensively studied in the orthopedic population. Using doses ranging from 0.025 mg to 2.5 mg for hip and knee surgery, ITM has been demonstrated to produce significantly better analgesia than controls in a dose dependent fashion; however, side effects occur with the higher doses[45-47]. The optimum dose appears to be around 0.1 – 0.2 mg. ITM has also been demonstrated to be effective in spine surgery with optimum doses being around 0.1 to 0.3 mg [28, 48, 49].

**Other Opioids**

Although less studied, the intrathecal delivery of other opioids has been used for the treatment of postoperative pain. These opioids offer the advantage of potentially less side effects due to higher lipid solubility than morphine; however, duration of analgesia is lessened. These other opioids have been used for a variety of surgical procedures. Fentanyl and sufentanil have been the most widely used. These drugs are highly lipid soluble thus significantly decreasing the incidence of side effects. In a double blind placebo controlled study, Sudarshan et al compared the effects of intrathecal fentanyl with saline and IV morphine. They concluded that intrathecal fentanyl resulted in better postoperative analgesia with no side effects [50]. In a double blind, placebo controlled study, Chilvers et al compared 0, 10 and 25 mcg of intrathecal fentanyl for gynecologic laparoscopy pain and determined that the 25 mcg dose provided better postoperative pain management with no difference in side effects [51]. In another dose response study, Reuben et al compared 0, 5, 10, 20, 40, and 50 mcg of intrathecal fentanyl for pain after lower extremity revascularization procedures. They concluded that 40 mcg was the optimal dose providing pain relief for approximately 5 hours with a low incidence of side effects [52]. Pruritis was the most common side effect with the 50 mcg dose. Fournier et al compared the analgesia and side effects of intrathecal fentanyl with intrathecal sufentanil in patients undergoing total hip replacement. They concluded that 40 mcg of intrathecal fentanyl provided similar analgesia and side effects as 7.5 mcg of intrathecal sufentanil [53]. In two studies on the use of intrathecal sufentanil for extracorporeal shock wave lithotripsy, Lau et al determined that sufentanil, at an optimum dose of 15 and 17.5 mcg, provided effective analgesia with few side effects. Their study demonstrated that sufentanil as a sole agent was as effective as 5% lidocaine for intraoperative analgesia for this procedure [54, 55].

**Epidural**

**Epidural Spread of LA**

In order to provide adequate analgesia covering a surgical incision the nerve roots for the appropriate dermatomes must be in contact with local anesthetic. Epidurally injected local anesthetic spreads in a cephalad and caudad fashion from the site of injection. Multiple factors affecting this spread have been investigated. A review of this
literature by Gielen (2008) showed that the factors are different for lumbar vs. thoracic epidurals [56]. The factors in question include:

- Total Mass of LA Injected: increasing but non-linear relationship. More evidence for total mass of LA regardless of volume than for volume alone
- Age: increased spread with age >60 in thoracic, equivocal increase in lumbar. Stronger association for motor block than sensory
- Height/Weight/BMI: conflicting or weak data
- Pregnancy: decreased LA required for a given level of blockade; onset of blockade is faster and more dense; cranial spread is greater than in non-pregnant
- Site of Injection: No difference in number of segments blocked between lumbar and high thoracic for a given volume of LA. High thoracic injection spread is more caudal, mid thoracic equal and low thoracic more cephalad.
- Patient Position: Lateral - 0-3 segments greater spread on dependent side. No difference in cranial spread supine to sitting. Trendelenburg 15 degrees pregnant patients – more cephalad spread and more rapid onset.
- Neck Position: contrast studies with catheter at T1-2 show minimal cranial spread with neck neutral or extended and significant cranial spread with neck flexed
- Needle bevel position: Injection through Touhy turned lateral or caudad does not alter spread of LA. Catheter position not reliably predicted by direction cephalad or caudad of needle bevel
- Speed of Injection: studies are equivocal
- Large volume Saline Injection: Using 5-10ml NS prior to LA in thoracic region resulted in 4 additional dermatomes covered with 1.5% mepivacaine but not with 1% mepivacaine – likely due to dilutional effect.

**Cervical**

Cervical epidural drug delivery is an uncommon procedure due to technical difficulties of accessing the cervical epidural space and fears of serious side effects. Although the technique of cervical epidural steroids is common practice, the literature supporting cervical epidural anesthesia and analgesia is sparse [57]-[58]-[62]. Nonetheless, several reports in the literature support the safety and efficacy of cervical epidural anesthesia and analgesia for neck and upper extremity surgeries.

Cervical epidural anesthesia for neck, shoulder and hand surgery has been reported to be an adequate and safe technique [63]. The largest report that has demonstrated the safety and efficacy of cervical epidural anesthesia is by Guo who performed a retrospective analysis of 763 patients who received cervical epidural anesthesia using different local anesthetic concentrations [64]. Many avoid this technique because of fear of inducing a bilateral phrenic nerve block and respiratory distress. Although this is a theoretical consideration, studies have shown that a clinically significant phrenic nerve block does not occur even with high concentrations of local anesthetic [65, 66]. However, actual phrenic nerve activities show a suppression of 72% and 57% of control value with 1% and 2% lidocaine, respectively [67]. In fact, cervical epidural anesthesia has been reported to relieve postoperative intractable hiccups [68]. Studies on the effect of cervical epidural anesthesia on respiratory function have failed to
show a significant effect on pO2, although most studies show a significant increase in pCO2 [69] [70].

The most common effect of cervical epidural anesthesia is a decrease in heart rate and blood pressure. There is also a blunted response to atropine and atropine-like drugs [71] [72] [73] [74] [75] [76]. Therefore, close hemodynamic monitoring should be done, and drugs for hemodynamic support should be readily available.

The most common surgery performed under cervical epidural anesthesia is carotid endarterectomy. It has been suggested that the use of regional techniques for carotid endarterectomy decrease perioperative morbidity. Studies on the use of cervical epidural anesthesia for carotid endarterectomy show similar results as for cervical plexus block [76] [75] [77] [78] [79] [80]. However, Goeau-Brissonniere et al concluded that a cervical plexus block is easier to perform, had less hemodynamic changes and was preferred over cervical epidural anesthesia [81].

**Thoracic and Lumbar**

The thoracic and lumbar delivery of analgesics is a widely used technique for the management of postoperative pain. There is an abundance of literature on these techniques; however, there are few well-controlled studies on the efficacy and outcomes of thoraco-lumbar analgesia for postoperative pain control. There are many “burning questions” surrounding the delivery of thoraco-lumbar analgesics for postoperative pain. These include: 1) Which is better, epidural morphine, control, or systemic morphine?, 2) Is morphine more efficacious when given by single bolus, or continuous infusion?, 3) Is there a difference in the efficacy of lumbar versus thoracic delivery of morphine and fentanyl?, 4) Is there an advantage to adding local anesthetic to the epidural opioid infusions? 5) What is the best drug to use for postoperative analgesia?

**Studies comparing epidural morphine with control and systemic morphine**

All of the controlled studies in the literature have demonstrated that epidural morphine results in a superior analgesia (Table 8 and 9). These studies may seem obvious but have demonstrated that the epidural delivery of morphine exerts a spinal action and when compared to control (i.e. saline injections), morphine is by far superior. Because of ethical reasons, all controlled studies allow rescue medicine; therefore, the controlled studies are actually a comparison to the systemic delivery of opioids. Although most studies comparing epidural morphine to systemic opioids show epidural morphine to be superior, there are some studies that have failed to show a difference. The negative studies appear to be weighted towards thoracic and upper abdominal surgeries. Rosenberg et al demonstrated that after upper abdominal surgery, the first request for additional analgesia was longer in the patients who received epidural morphine versus intramuscular morphine (7.5 vs. 3.5 h); however, at 24 h, there was no difference in the efficacy rating between methods [84]. Two studies have demonstrated a significant benefit of single shot epidural morphine over systemic morphine after upper abdominal surgery [85, 86].
Study results on the continuous infusion of epidural morphine versus systemic analgesics for thoracic and upper abdominal surgery are even more conflicting. In thoracotomy patients, James et al showed no difference between 150 mg IV tramadol and epidural morphine [87]. Likewise, Larsen et al demonstrated no difference between repeated epidural boluses of morphine as compared to subcutaneous morphine after thoracotomy [88]. On the other hand, several studies have demonstrated that continuous epidural morphine is superior to systemic analgesics after thoracic and upper abdominal surgery [89-92].

Whereas studies on the use of epidural morphine for thoracic and upper abdominal surgery show conflicting results, the epidural delivery of morphine for lower abdominal and orthopedic surgery consistently show superior results over control and systemic opioids (Table 8 and 9). Once exception is a study by Stevens et al who compared thoracic epidural morphine to systemic morphine for the treatment of postoperative pain after radical prostatectomy. They failed to show any differences in the quality of analgesia between groups [93]. The failure to show a difference may be related to the fact that they used a thoracic epidural rather than a lumbar epidural.

**Studies comparing a single bolus with a continuous infusion of epidural morphine**

The single epidural bolus delivery of morphine has been demonstrated to have an analgesic duration of up 24 hours. Therefore, it is reasonable to assume that a single bolus should be as effective as a continuous infusion of morphine. There are very few studies, which have made this comparison. Fujikawa et al showed that a single bolus of morphine was no different than a continuous infusion of epidural morphine for up to 12 hours after laparoscopic cholecystectomy [94].

**Studies on the effect of adding local anesthetic to epidural morphine infusions**

Balanced analgesia is defined as administering different agents together that affect different physiologic processes involved in nociception. Therefore, it is reasonable to assume that the co-administration of a local anesthetic (which inhibits transduction of nociception) and an opioid (which inhibits modulation of nociception) will result in overall better analgesia. Studies on thoracic, upper abdominal and lower abdominal surgery have clearly demonstrated the advantages of the co-administration of opioid and local anesthetics over opioids alone [95, 96] or local anesthetics alone [96-99]. When comparing epidural local anesthetics alone versus epidural morphine there appears to be an advantage of the epidural local anesthetic after hip and knee surgery [100, 101], conflicting reports after lower abdominal surgery [97, 102] and no differences after thoracotomy and upper abdominal surgery [90, 96].

**Studies on the lumbar versus thoracic epidural delivery of morphine for thoracotomy and upper abdominal surgery**

Because morphine is hydrophilic, it should spread throughout the neuraxis resulting in analgesia at dermatomes distant from the site of delivery. Therefore, the location of epidural delivery should not influence the resulting analgesia regardless of the location of the surgery. There are numerous studies comparing the lumbar and thoracic epidural delivery of morphine with conflicting results. After thoracotomy, there appears...
to be an advantage of thoracic epidural morphine over lumbar epidural morphine. In a group of post thoracotomy patients who received as needed boluses of thoracic or lumbar epidural morphine, it was demonstrated that although pain scores were similar between groups, the thoracic group required less morphine [103]. Yang et al demonstrated that after thoracotomy the thoracic delivery of morphine resulted in an earlier onset of analgesia as compared to the lumbar delivery but there was no differences in pain relief beyond 50 minutes [104]. Finally, Rodriguez-Huertas et al showed that after thoracotomy, the total epidural dose of a bupivicaine/morphine mixture was higher in the lumbar groups as compared to the thoracic groups. Therefore, there appears to be an overall advantage to delivering morphine via thoracic route as compared to the lumbar route after thoracotomy.

On the other hand, studies after upper abdominal surgery have had conflicting results. After abdominal aortic aneurysm repair, Gold et al demonstrated a significant decrease in pain scores during the first 36 hours in the lumbar delivery group; however, there were no differences in total morphine requirements [105]. Two studies after upper abdominal surgery have failed to show a difference between the lumbar versus thoracic epidural delivery of morphine [106, 107].

Whereas morphine is a hydrophilic drug and should spread throughout the neuraxis, fentanyl and sufentanil are lipophilic drugs that should severely limit the dermatomal spread after epidural delivery. Therefore, if lipophilic drugs are acting via a spinal mechanism, the delivery of these agents close to the site of the surgery should be advantageous. However numerous studies in thoracotomy patient have failed to show any difference in analgesia with the lumbar versus thoracic delivery of fentanyl [108-111]. Similar results have been demonstrated using sufentanil in upper abdominal surgery[112]. These studies suggest that the analgesia resulting from the systemic absorption of the lipophilic agents outweighs the spinal effect. Sawchuck et al demonstrated in post thoracotomy patients that although pain scores were similar between groups, the lumbar delivery of fentanyl required higher infusion rates than the thoracic delivery [113]. The influence infusion rates on efficacy of the lipid soluble agents has been studied with conflicting results[114, 115]. In a study comparing lumbar morphine/bupivicaine and thoracic fentanyl/bupivacaine, Kahn et al determined that the thoracic epidural fentanyl/bupivacaine resulted in superior analgesia [116]. This study suggests that there is both a spinal and systemic effect of thoracic epidural fentanyl. Finally, Chisakuta et al determined that thoracic epidural delivery of fentanyl/bupivacaine was superior to the lumbar delivery of fentanyl/bupivacaine after upper abdominal surgery[117].

Clonidine

The clearest advantage of clonidine is when co-administered with an opioid. Numerous studies have demonstrated an advantage of combining clonidine with an opioid over an opioid or clonidine alone after thoracic/upper abdominal surgery [118-124]. Two studies after orthopedic surgery have shown different results. After hip surgery, Carabine et al demonstrated that the continuous delivery of morphine/clonidine was superior over morphine or clonidine alone [125]. In contrast, van Essen et al showed
no advantage of a single dose of clonidine/opioid combination over opioid or clonidine alone after knee surgery. However, they administered the dose one hour after the surgery thus precluding the preemptive analgesia of the drug [126].

Although epidural clonidine appears to provide better analgesia than local anesthetic alone after abdominal [127] and orthopedic surgery [128], epidural clonidine is inferior to an opioid/local anesthetic combination after upper abdominal [129] and lower abdominal [130, 131].
TABLE 8: Comparison of Single Shot Epidural Morphine with Other Techniques for Postoperative Pain Management

<table>
<thead>
<tr>
<th></th>
<th>vs. control</th>
<th>vs. systemic opioids</th>
<th>vs. continuous opioids</th>
<th>vs. continuous LA + opioid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thoracotomy</td>
<td>+[24, 132]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Abdominal</td>
<td>+[94, 133-135]</td>
<td>+[85, 86]</td>
<td>0[94]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0[84]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower Abdominal</td>
<td>+[135-139][Shapiro, 1981 #547][140]</td>
<td>+[141-143]</td>
<td></td>
<td>-[95]</td>
</tr>
<tr>
<td>Orthospine</td>
<td>+[144-148]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ortho lower extremity</td>
<td>+[150-154]</td>
<td>+[153, 155-158]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

+ = significantly superior 0 = no difference; - = significantly inferior
<table>
<thead>
<tr>
<th></th>
<th>vs. control</th>
<th>vs. systemic opioids</th>
<th>vs. continuous LA + opioid</th>
<th>vs. continuous LA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thoracotomy</td>
<td>![159]</td>
<td>![89] [90] [91]</td>
<td>![88] [87]</td>
<td>![90]I</td>
</tr>
<tr>
<td>Upper Abdominal</td>
<td>![94, 160]</td>
<td>![92]</td>
<td>![96]</td>
<td>![96]</td>
</tr>
<tr>
<td>Lower Abdominal</td>
<td>![93]</td>
<td></td>
<td></td>
<td>![97]</td>
</tr>
<tr>
<td>Orthospine</td>
<td>+[161]</td>
<td>![162, 163]</td>
<td></td>
<td>![102]</td>
</tr>
<tr>
<td>Ortho lower extremity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

+ = significantly superior 0 = no difference; - = significantly inferior
TABLE 10: Comparison of Continuous Epidural Morphine + Local Anesthetic with Other Techniques of Postoperative Pain Management

<table>
<thead>
<tr>
<th></th>
<th>vs. control</th>
<th>vs. systemic opioids</th>
<th>vs. continuous LA</th>
<th>vs. continuous opioid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thoracotomy</td>
<td>+[159]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Abdominal</td>
<td>+[164-166]</td>
<td>+[167-169]</td>
<td>+[96, 98, 99]</td>
<td>+[96]</td>
</tr>
<tr>
<td>Lower Abdominal</td>
<td></td>
<td></td>
<td></td>
<td>+[97]</td>
</tr>
<tr>
<td>Orthospine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ortho lower extremity</td>
<td></td>
<td></td>
<td>+[170-172]</td>
<td></td>
</tr>
</tbody>
</table>

+ = significantly superior 0 = no difference; - = significantly inferior
REFERENCES:


22. Neal, Joseph M. MD*; Bernards, Christopher M. MD*; Butterworth, John F. IV MD†; Di Gregorio, Guido MD‡; Drasner, Kenneth MD§; Hejtmanek, Michael R. MD*; Mulroy, Michael F. MD*; Rosenquist, Richard W. MD||; Weinberg, Guy L. MD. Asra Practice Advisory on Local Anesthetic Systemic Toxicity. Regional Anesthesia & Pain Medicine: March/April 2010 - Volume 35 - Issue 2 - pp 152-161


96. Crews, J.C., et al., *A comparison of the analgesic efficacy of 0.25% levobupivacaine combined with 0.005% morphine, 0.25% levobupivacaine alone, or 0.005% morphine alone for the management of postoperative pain in patients undergoing major abdominal surgery.* Anesthesia and Analgesia, 1999. 89(6): p. 1504-9.


OVERVIEW OF CHRONIC PAIN

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OVERVIEW OF CHRONIC PAIN

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INTRODUCTION

With advances in knowledge on the pathophysiology of pain, we have greatly improved our ability to treat chronic pain. It has been estimated that in the United States almost $80 billion is spent annually on chronic pain. Approximately 80 million Americans (one-third of the population) suffer from chronic pain, and 433 million workdays are lost annually due to pain. Yet education on pain management has a low priority in most medical school curricula leading to the general undertreatment of chronic pain.

The pain experience can be described in terms of three components: 1) sensory, 2) emotional, and 3) cognitive. Sensory: The sensory component is controlled by our nervous system. If I hit my thumb with a hammer, this will activate the nervous system which sends messages to the brain. The brain will then analyze these messages and tell us where it hurts and how much it hurts. It is a system that usually is turned on in times of tissue injury and turned off when the tissue heals. However, in some patients with chronic pain, this system turns on and remains turned on even in the absence of any tissue damage. Physicians can control the sensory component with medications, physical therapy and nerve blocks. Emotional: When pain activates our sensory nervous system, the sensory nervous system will in turn activate structures deep within our brain which control our emotions, heart rate, and blood pressure. If a child experiences pain, the immediate reaction is to cry. This is because children have minimal control over their emotions. Adults may react by becoming withdrawn or depressed. Physicians can control the emotional component with medications. A psychologist can teach the patient biofeedback techniques to decrease the emotional response. Cognitive: Our culture or past experience with pain can determine how we respond to pain. A child that experienced pain during development may be extremely afraid of pain as an adult. In addition, some cultures accept the outward expression of our emotions whereas others promote the idea that we should keep things inside and not bother people with our problems. A psychologist can be very effective in analyzing past experiences and assist the chronic pain patient in coping.

There are many different treatments of pain which include pharmacologic, psychological, rehabilitative, interventional, and alternative. The method used will depend on the underlying etiology of the pain as not all pain is the same. If the nervous system is functioning properly and the pain is secondary to tissue damage such as muscle strains, arthritis, acute low back strains, the pain is quite responsive to simple pain relievers such as ibuprofen, acetaminophen, or mild opioids. However, if the nervous system is injured such as after surgery or trauma, the injured nerve will report its own pain leading to a type of pain called neuropathic pain. Neuropathic pain can be very refractory to common pain relievers. Through our knowledge of how pain pathways function in the body, we have determined that neuropathic pain is better treated with drugs such as antidepressants, anticonvulsants and certain blood pressure medicines. In very refractory cases, the patient may require chronic opioids for pain relief.
Pain can also cause the individual to avoid activities that may increase the pain. This may result in a significant reduction in normal daily activities that can lead to increase muscle spasms, stiff joints and increased pain. Therefore, physical therapy can be very helpful in many chronic pain patients.

If the patient continues to have uncontrolled pain after reasonable attempts with medications and exercise, psychological counseling can be very helpful in assisting the patients with coping skills. Biofeedback and relaxation techniques are also effective in relieving chronic pain.

Some patient will benefit from interventional techniques such as spinal injections or nerve blocks. These treatments usually do not provide long-term relief and should be done in conjunction with a total pain management program. In extremely refractory cases, drugs may be infused into the spinal column which block pain pathways and result in pain relief. In addition, electrodes can be implanted in the spinal column which stimulate the spinal cord and replace the painful area with a tingly sensation. These are very invasive procedures that require surgical implantation. Careful patient selection is required.

Finally, alternative techniques may be helpful in the management of pain which include acupuncture and chiropractic adjustment. These techniques often require repeated treatments.

A. Introduction
   1. In the United States - $80 Billion spent annually on chronic pain
   2. Approximately 80 million Americans (one-third of the population) suffer from chronic pain
   3. 433 million work days are lost annually due to pain
   4. Many physicians are uncomfortable with pain management

B. Categories of Pain
   1. Nociceptive – Pain that is transmitted through a normal functioning nervous system
   2. Neuropathic – Pain that is transmitted through an injured nervous system

C. Neuropathic Pain
   1. Pain in the absence of detectable tissue injury
   2. Abnormal or unpleasant sensation
   3. Burning or electrical quality of the pain
   4. Pain in an area of sensory deficit
   5. Minimal stimulation is painful
   6. “Wind-up”

D. Examples of Pain Syndromes

<table>
<thead>
<tr>
<th>Nociceptive</th>
<th>Neuropathic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Pain</td>
<td>Cancer Pain</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Low Back Pain</td>
</tr>
<tr>
<td>Cancer Pain</td>
<td>Post-mastectomy Pain</td>
</tr>
<tr>
<td>Headache</td>
<td>Peripheral Neuropathy</td>
</tr>
<tr>
<td>Post-operative Pain</td>
<td>Reflex Sympathetic Dystrophy</td>
</tr>
<tr>
<td>Sickle Cell Crisis</td>
<td></td>
</tr>
</tbody>
</table>
E. Mechanisms of Neuropathic Pain
   1. A-beta sprouting into Lamina II (C fiber terminal region)
   2. Sympathetic fiber sprouting onto large type A dorsal root ganglion cells
   3. Loss of dorsal horn inhibitory interneurons

F. Methods of Chronic Pain Management
   1. Pharmacologic
   2. Psychologic
   3. Physical methods
   4. Interventional techniques
   5. Alternative techniques

G. Pain Treatment Continuum
   Over the counter drugs ➔ nonsteroidal antiinflammatory drugs ➔ physical therapy, manipulative medicine, acupuncture, transcutaneous electrical nerve stimulation ➔ muscle relaxants ➔ oral analgesics/narcotics ➔ therapeutic nerve blocks ➔ diagnostic/prognostic nerve blocks ➔ behavioral programs ➔ radiofrequency lesioning ➔ surgery ➔ spinal cord stimulation ➔ spinal drug delivery ➔ destructive neurosurgical procedures

H. Pharmacologic methods
   1. Analgesic Efficacy for Nociceptive vs Neuropathic Pain
      Nociceptive        Neuropathic
      Opioids            Antidepressants
      NSAIDs             Anticonvulsants
      Acetaminophen      Antiarrhythmics
      Tramadol           Alpha 2 agonists

   2. Tolerance
      a. Reduction in effect produced by a given dose of drug, or an increase in the dose required to produce a given analgesic effect
      b. Minimal cross-tolerance between drugs that act at different receptors
      c. Asymmetric tolerance between drugs that act at the same receptor but with differing intrinsic activities
      d. Causes of increased tolerance:
         - Pharmacokinetic changes
         - Changes in pain intensity
         - Changes in pain mechanism
         - Changes in the psychologic state of the patient
         - Pharmacodynamic changes (tolerance)

   3. Dependence
      a. Physical
         - Abrupt cessation of the drug will cause withdrawal symptoms
         - Easily reversed
      b. Psychological
         - Compulsive drug use and drug hoarding
         - Very rare outcome in pain patients
4. Addiction
   a. Studies report incidence ranging from 0.03% - 24%
   b. Wide range likely the result in differences in definition of addiction
   c. DSM-IV criteria for substance abuse cannot be used to diagnose addiction in pain patients because 5 of the 9 criteria refer only to physical dependence and tolerance which can occur in long-term opioid treatment
   d. Bottom line: Incidence very low in the chronic pain patient population

5. New agents on the horizon
   Adenosine Kinase inhibitors
   Botulinum toxin
   Cox-2 inhibitors
   Prostaglandin E antagonists
   Glycine antagonists
   NK1 antagonists
   N-type calcium channel antagonists

   Nicotinic receptor agonists
   New opioids
   Alpha 2 agonists
   IV acetaminophen
   Prosaposins
   Sodium channel antagonists

I. Psychologic methods
   1. Coping skills
   2. Individual counseling
   3. Group therapy (support groups)
   4. Biofeedback
   5. Relaxation
   6. Educational series

J. Physical methods
   1. Physical therapy
   2. Massage
   3. Stimulatory techniques
      a. Transcutaneous electrical nerve stimulation
      b. Transcutaneous electrical muscle stimulation
      c. Dorsal column nerve stimulation

K. Interventional Treatments
   1. Neural Blockade
      a. Diagnostic blocks
         - Used to identify the pain generator
      b. Prognostic blocks
         - Used to determine if definitive procedure is indicated
      c. Therapeutic blocks
         - Prolonged pain relief with single series
         - In conjunction with physical therapy
   2. Neuolytic techniques
      a. Less effective for neuropathic pain
      b. Reserved for refractory cases/cancer pain
      c. Radiofrequency lesioning
         - High temperature lesioning
         - Low temperature pulse radiofrequency lesioning (preserves sensory motor function, low risks)
d. Cryoanalgesia
   - Less likely to develop neuritis

e. Chemical Ablation
   - Phenol, alcohol
   - Commonly used for plexus blocks (i.e. celiac, hypogastric) and subarachnoid
     blocks

3. Stimulatory techniques
   a. Dorsal Column Nerve Stimulation
      - Epidural placement of electrode which stimulates dorsal column tracts
      - Positioning of electrode so that the area of stimulation corresponds to the pain.
      - 60-70% long-term efficacy
      - Battery life of generator is approximately 4-5 years.

4. Intraspinal Drug Delivery
   a. Delivery of drugs that bind to receptors or ion channels in the dorsal horn of the
      spinal cord
   b. Ion channel blockers
      - Ziconotide (N-type calcium channel blocker)
      - Bupivacaine (Sodium channel blocker)
   c. Receptor Agonists
      - Opioids (mu, kappa, delta receptor agonists)
      - Clonidine (alpha 2 adrenoreceptor agonist)
      - Baclofen (GABA-B receptor agonist)
   d. Drug mixtures

5. Alternative methods of pain control
   a. Acupuncture
   b. Chiropractic
   c. Therapeutic touch
   d. Herbal homeopathic medicine

Selected Readings
Irving G, Wallace M. Pain Management for the Practicing Physician, Churchill Livingstone,

CHRONIC OPIOID THERAPY: ACHIEVING SUCCESS & AVOIDING PITFALLS

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INTRODUCTION
Chronic opioid therapy is widely accepted as the first-line treatment for moderate to severe cancer-related pain. Opioids are also an important part of treatment of many intractable non-malignant chronic pain states. Systematic application of simple guidelines for chronic opioid therapy has been shown to result in a favorable outcome in as high as 90% of patients with malignant pain, although in clinical practice this high rate of success is rarely realized either with malignant or non-malignant pain. Under-treatment has been identified as one of the leading causes of treatment failure. However, even if under-treatment were eliminated, chronic opioid therapy, particularly for management of chronic non-malignant pain, offers numerous challenges that may interfere with long-term success. Impediments to the successful use of opiates for management of chronic pain disorders may be secondary to drug-related factors or may be related to barriers at the patient, physician and healthcare system levels.

DRUG-RELATED FACTORS
Opioid responsiveness may be defined as the probability that adequate analgesia (satisfactory relief without intolerable and unmanageable side effects) can be attained during gradual dose titration. An alternative definition may be the degree of analgesia obtained at treatment-limiting toxicity. Unfortunately, there is tremendous variability in the responsiveness of each patient to different opioids and in the responsiveness of different patients to the same opioid. Mechanisms that underlie this variability are multi-factorial. Some of the more common factors have been investigated. Neuropathic pain states and the presence of severe breakthrough pain are examples of pain states that reduce opioid responsiveness. Alternatively, advanced age and major organ failure are health-related factors that predispose patients to opioid side effects and lead to decreased success with this therapy. Extensive clinical observation has failed to identify any characteristic of the pain state or of the patient’s health status that is so predictive that either negative or positive outcomes can be known in advance of a therapeutic trial. Further-more, the within-patient responsiveness to different opioids varies to such an extent that a poor response to one drug should not be interpreted as a poor response to opioid therapy overall.

STRATEGIES TO OVERCOME DRUG-RELATED FACTORS
Opioid responsiveness should be monitored throughout the initiation and maintenance phases of chronic opioid therapy by assessing the balance between efficacy and adverse effects. For patients with relatively stable pain levels, a single long-acting opioid is generally adequate. Some patients will require rescue doses of short-acting opioids for ‘breakthrough pain’. In cases where gradual opioid dose escalation does not result in a favorable balance between analgesia and adverse effects, the possibility of poor responsiveness to the specific agent used or the route of administration should be considered. For patients exhibiting poor opioid responsiveness, a number of strategies may be used to maximize treatment benefit.

Opioid Rotation
The goal of opioid rotation is to identify the opioid with the most favorable balance between analgesia and side effects for a particular patient. Opioid rotation involves sequential administration of various opioid agents over time. Each new agent is administered on a trial basis. The patient undergoes a titration phase until either efficacy or side effects are
reached. The titration phase is followed by a maintenance phase, if a favorable balance between analgesia and side effects is achieved. Opioid rotation is now considered a standard clinical approach in chronic opiate therapy. Safe and successful opioid rotation requires knowledge of equianalgesic doses of these agents. Equianalgesic dose tables are available in commonly used reference texts. These charts may be used as a general guide for dose selection when rotating from one opioid to another. However, the calculated dose must be modified based on each individual patient’s age, comorbidities, prior exposure to opioids and the clinician’s experience.

**Pharmacological Strategies**

Three main pharmacological strategies may allow a poorly responsive patient to achieve a more favorable balance between opioid efficacy and side effects. These include co-administration of non-opioid analgesics, co-administration of adjuvant analgesics and the use of alternative modes of drug delivery.

Non-opioid medications that reduce the patient’s pain level or increase the potency of the opioid may reduce the total opioid requirement. The most common non-opioid analgesics include acetaminophen, NSAIDS and the cyclooxygenase-2 selective inhibitors (COX-2). This strategy is particularly helpful in patients with co-existing somatic and neuropathic pain components. For example, a patient with osteoarthritis involving the lumbar facet joints and the hip and an L5 radiculopathy may get good relief of the back and hip pain with an NSAID, but may require a different mode of therapy for the radiculopathy. Although COX-2 inhibitors are no more effective than the NSAIDs, they may be more cost effective in certain populations such as the elderly or patients with end organ pathology.

Adjuvant analgesics are medications that may have analgesic properties in a specific diagnosis but have a primary indication other than pain. A large number of medications in numerous classes may be used for this purpose. Examples include: antidepressants, α-2 adrenergic agonists, anticonvulsants, sodium channel antagonists, topical agents and corticosteroids. The most common indication for the use of adjuvant analgesics is the presence of neuropathic pain.

Gabapentin, an anticonvulsant, is currently the most common adjuvant agent used for neuropathic pain. The most common reason for lack of success with this medication is failure to titrate the dose to an adequate level. Many patients may not reach efficacy until a 3000-3600 mg daily dose is reached and some may not respond until a dose of 6000 mg per day is reached. Gabapentin does not undergo hepatic metabolism and has no known interactions with other drugs. Other anticonvulsants used for neuropathic pain include carbamazepine, phenytoin, divalproex and clonazepam, and the newer agents lamotrigine, topiramate, tiagabine, oxcarbazepine, zonisamide and levetiracetam.

The tricyclic antidepressants amitriptyline, nortriptyline, doxepin, imipramine and desipramine all have a long history of use as adjuvants and have been well studied. Analgesic evidence for the newer selective reuptake inhibitors is more anecdotal.
The alfa-2 adrenergic agonists clonidine and tizanidine have been shown to be analgesic in a variety of conditions. Besides their role as analgesics, these may be used to manage symptoms of opioid withdrawal. They may also be administered neuraxially for neuropathic pain.

Systemic administration of local anesthetics may provide analgesia in refractory neuropathic pain. However, achieving long-term success with this approach is challenging even in experienced hands. Oral local anesthetics have also been used including mexilite, flecanide and tocanide. The favorable side effect profile of gabapentin and its lack of interaction with other drugs have lead to a dramatic reduction in the use of the oral local anesthetics that tend to have less favorable side effect profiles.

Baclofen is a GABA agonist that may be helpful in a variety of neuropathies, particularly trigeminal neuralgia. It is also helpful in the treatment of muscle cramps and spasm associated with radiculopathies. It may be administered orally or neuraxially; the effective dose range varies widely.

Topical or transdermal delivery systems of local anesthetics, NSAIDs and capsaicin may provide an additional method of pain relief complementing the chronic opioid therapy. Lidocaine is available in a transdermal patch approved for postherpetic neuralgia. It is being evaluated for a variety of other neuropathic processes. Lidocaine is also available in a cream form (a eutectic mixture of lidocaine and prilocaine) and pure lidocaine gel, cream and ointment. These forms of the drug are helpful in a variety of malignant pain conditions but are less commonly used in chronic non-malignant pain.

Topical NSAIDs can be very effective for arthropathies and soft tissue pain. Topical application of capsaicin has been shown to be helpful in neuropathies of peripheral origin but the failure rate is high because of lack of compliance.

**Aggressive Side-Effect Management**

Adequate management of opioid side effects may in many cases allow further titration of a drug such that a poorly opioid responsive patient may achieve a favorable balance between efficacy and side effects. Side effect management should be a routine part of any drug therapy, especially opioids. Constipation is the most common side effect of opioids requiring treatment. Generally, it may be managed effectively with a combination of dietary changes, bulking agents and stool softeners. Promotility agents and osmotic agents may be necessary in some cases. Mild pruritis can usually be controlled with hydroxyzine, but more severe cases may require rotation to an alternative opioid. Edema is a rare side effect of opioids that may be difficult to control without rotation to an alternative agent. Urinary retention will improve over time in many cases, but may require lowering of the opioid dose initially and a slower titration to an effective dose.

Management of opioid-induced somnolence and cognitive impairment in chronic non-malignant pain is more controversial. Psychostimulants are used in the cancer population with some frequency to allow for further titration of opioids. In this population, however, most patients on chronic opioid therapy no longer drive, work or have other home or social
responsibilities. For patients with chronic non-malignant pain these issues may play a pivotal role. Each case must, therefore, be evaluated individually to determine if psychostimulants may be indicated. All other strategies must be exhausted before psychostimulants are considered. The risks of further contributing to the patient’s polypharmaceutical regimen must also be considered.

The guidelines for use of psycho-stimulants are empiric. There are no studies comparing the various stimulants. Whichever agent is selected should be started at the lowest dose and gradually titrated to effect. If the therapeutic response is poor or not sustained with modest dose increases, then the patient should be rotated to a different stimulant agent.

Non-Pharmacological Strategies

Interventional techniques in pain medicine such as nerve blocks, neuroablative and neuroaugmentative techniques represent the mainstay of non-pharmacological strategies. A number of other non-pharmacological strategies should also be considered, including: therapeutic exercise, physical and occupational therapy, orthotics and bracing techniques, osteopathic techniques, acupuncture and cognitive behavioral and psychoeducational therapies.

PATIENT RELATED BARRIERS

Patient-related obstacles to chronic opiate therapy center on communication, attitudinal and psychological issues and issues related to substance abuse. Patients who report communication problems with their healthcare providers also report higher pain levels than those who did not have difficulty communicating. Pre-existing attitudes may also cause impediments to successful pain management and particularly chronic opiate therapy. Patients may be reluctant to report pain because of stoicism or fear that increasing pain may indicate worsening disease. Concerns about addiction and medication side effects are common causes of miscommunication. Social stigma about drug use may lead to individual or family pressure to avoid or discontinue opioid therapy. Within the geriatric population, myths about chronic opioids are common. Pain is sometimes viewed as a sign of weakness or may be thought of as a normal part of the aging process, something that should simply be tolerated.

Psychological states such as depression, anxiety and dementia may influence therapy either by masking or exaggerating a patient’s symptoms. Anger may also lead to symptom exaggeration. Why anger exists and who it is aimed at must be understood so that it can be appropriately redirected to promote a healthy therapeutic relationship. Personality disorders, however, may be the most challenging of the patient-related obstacles to chronic opiate therapy. Borderline personality disorder poses the greatest challenge. The course of chronic opiate therapy for patients with antisocial, histrionic and narcissistic personality disorders, although demanding, is rarely as stormy as that of the borderline patient. In management of patients with psychological co-morbidities and particularly with personality disorders it is important for the clinician to be cognizant of his or her own feelings toward the patient. For example, the clinician may feel sadness or apathy when dealing with depression and agitation and a feeling of alarm in response to anxiety disorders. A sense of fear may indicate antisocial personality disorder.
Management of chronic opioid therapy in patients with borderline personality disorder appears to pose a special challenge. Borderline personality disorder has been characterized as ‘stable instability’, which is pervasive within the patient’s relationships, affect, mood and even sense of identity. Individuals with borderline personality disorder suffer from chronic feelings of emptiness. They may go to extreme measures to avoid abandonment whether real or imagined. This may explain their impulsive and self-destructive behaviors. Recurrent suicidal behavior and intense anger are not uncommon. Borderline patients repeatedly test their boundaries and push the limits. This is not limited to the physician. Rather, their behavior extends to all of the office personnel and may precipitate conflict between various members of the therapeutic team. This manipulative behavior has been referred to as ‘splitting’.

Manipulative behavior is a common presentation in patients with personality disorders. In many cases the manipulative behavior is based in fear of not having their needs met. The patient, however, may or may not be aware of these needs. Therefore, it is crucial to determine what the patient is afraid of and to help the patient understand those needs. Once a better understanding of the patient’s personality traits is achieved, the clinician can now appeal to the patient in a manner that she or he can more readily relate to and communication is facilitated. For example, with the angry patient the clinician may empathize by saying: “Sometimes I get really frustrated with the system, too… what can we do together to meet your needs?” In contrast, for the fearful patient the clinician may say: “I agree with you that you need… let’s see if we can figure out how/where to get it.” For the entitled patient the approach may be: “I hear you that you need… let’s look at what is possible.” The ultimate goal is to meet the patient’s needs as much as possible or appropriate. This should lead to a reduction or cessation of the manipulative behavior.

In dealing with the manipulative patient with personality disorder, follow the basic principles of soft-spoken limit setting. Always remain calm. That is why it is important to be aware of your feelings for the patient. Connect with the patient empathically. But do so without losing your objectivity. Give the patient choices. That is, clearly define the appropriate therapeutic options they may select from. But maintain the patient’s responsibility for decision-making. Finally, restore control. Remain focused on the basic principles and redirect the patient towards the acceptable therapeutic boundaries.

SUBSTANCE ABUSE

There is concern within the medical community regarding misuse of analgesic drugs. Currently, 6.3% of the U.S. population uses illicit drugs or prescription drugs for non-medical reasons. Prescription drugs are used for non-medical reasons in 1.2% of the U.S. population. Achieving a balance between appropriate management of chronic intractable pain and prevention of prescription drug abuse is an important and challenging task. However, recent data does indicate that the increase in the use of opioids to treat pain has not resulted in a higher incidence of analgesic abuse.

Opioid therapy carries a low risk of abuse and addiction in patients with no prior history of substance abuse. Appropriate use of opioids for chronic intractable pain generally results in improved function, such as fulfillment of family, social and vocational
responsibilities, in association with decreased pain levels. Patients seldom describe euphoria and do not engage in aberrant drug-related behavior. In contrast, individuals with substance abuse generally show a decline in function and ability to fulfill obligations.

**Abuse Nomenclature**

A great deal of the confusion and hesitation regarding chronic opioid therapy is related to misunderstanding and incorrect usage of terminology by the medical community. It is crucial to understand and distinguish between such terms as addiction, pseudoaddiction, physical dependence, abuse and tolerance. Inappropriate classification of patients not only leads to failure in treatment but may also stigmatize the patient leading to serious personal, social and vocational impact.

**Tolerance**

Tolerance is the need for increasing doses of a drug to maintain the same level of efficacy over time. Tolerance to various effects of opioids may occur at different rates. For example, tolerance to nausea may develop soon after an opioid is started, but tolerance to constipation may persist for much longer periods. The term tolerance does not apply if the increased dose requirement is caused by progression of disease. An alternative definition of tolerance is: a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug’s effects over time.

**Physical Dependence**

Physical dependence is a state of adaptation that is manifested by a drug-class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction or decreasing blood level of the drug, or administration of an antagonist. ‘Physical dependence’ is not synonymous with ‘substance dependence’, ‘drug dependence’ or ‘addiction’. Physical dependence may occur with minimal opioid exposure. The dose or a duration of opioid exposure required to produce clinically significant physical dependence in not known. Opioid withdrawal syndrome should not be confused with addiction.

**Abuse**

Substance abuse is defined as the use of a substance in a manner outside of sociocultural conventions. This includes the use of illicit drugs and the use of medications for nonmedical purposes and against a physician’s prescription.

**Addiction**

Addiction, also referred to as psychogenic dependence, has been the most difficult term to define. It is felt to be a primary, chronic neurobiological disease, with genetic, psychosocial and environmental factors influencing its development and manifestations. It is characterized by one or more of the following behaviors: impaired control over drug use, compulsive use, continued use despite harm, and craving. Within the chronic pain population, it is most appropriate to make the diagnosis of addiction based on observation of these aberrant behaviors rather than the presence of tolerance or physical dependence (abstinence syndrome).
Pseudoaddiction

Pseudoaddiction was defined in 1989 to describe an iatrogenic syndrome of aberrant behavior as a direct result of inadequate pain management. The cardinal feature of this syndrome is that the aberrant behaviors disappear when pain is adequately treated.

ABERRANT DRUG-RELATED BEHAVIOR AND ADDICTION

Each chronic pain patient’s evaluation must include assessment of the risk for abuse and addiction before an optimal treatment strategy can be developed. The risk of aberrant behavior is low among patients with no history of substance abuse. Patients with a prior history of substance abuse who are not suspected to abuse opioid prescription drugs generally have few aberrant behaviors. They are more likely to be members of Alcoholics Anonymous or Narcotics Anonymous and to have stable family or other support systems. The risk of aberrant behavior in the chronic pain population is probably highest among patients with ongoing substance abuse. Doctor shopping, frequent dose escalations and frequent telephone calls to the clinic are some of the most common aberrant behaviors. Others include prescription loss, visiting without an appointment, multiple drug allergies or intolerances, stealing drugs from others, obtaining drugs from non-medical sources, prescription forgery, selling prescription drugs, injecting oral formulations, non-compliance despite multiple warnings, resistance to changes in therapy despite evidence of adverse effects and drug-related functional deterioration at work and home.

Patient Assessment

It is important for physicians to become comfortable with discussing substance abuse issues. An open, frank and professional demeanor, and treatment of the patient with respect and empathy will help evoke truthful responses from the patient. The discussion may be started with caffeine, nicotine and alcohol and then proceed with illicit drugs. Documentation is important and should include all medications and drugs and their amounts, chronology of use, frequency of use and the triggers that usually initiate their use. Patients should also be asked about the desired effects of each drug used. This may provide information about coexisting mood disturbances.

Psychiatric Co-morbidities

Fifty-three percent of individuals with a lifetime diagnosis of a substance abuse disorder (excluding alcohol abuse) also have a lifetime diagnosis of a mental disorder. The most common co-morbid disorders include antisocial personality disorder, conduct disorder, manic episodes in bipolar disorder, and schizophrenia. Major depressive disorder, anxiety disorder, and attention deficit/hyperactivity disorder are also sometimes co-morbid with substance abuse. Patients with both substance abuse and psychiatric disorders tend to have the highest treatment failure rates partly due to their lack of compliance and partly due secondary to their inability to receive comprehensive treatment in one program. This underlines the need for a multi-disciplinary approach for treatment in this patient population.

Genetic and Environmental Influences

A family history of substance abuse has been cited as one of the most important risk factors for the development of substance abuse among exposed offspring. Social and cultural
factors may also contribute to this increased risk. These complex interactions must be realized and considered when establishing a treatment plan for the chronic pain patient with coexisting substance abuse disorder.

**RISK-BASED THERAPEUTIC STRUCTURE**

Chronic opioid therapeutic strategies fall along a continuum of increasing degrees of structure and supervision. The therapeutic strategy must be individualized for each patient and it must be re-evaluated periodically for appropriateness. On one end of the continuum, the patient with no personal or family history of substance abuse may require minimal structure and monitoring. Opioid treatment may consist of both a long-acting opioid and a short-acting agent for breakthrough pain. The patient with psychiatric co-morbidities or past history of substance abuse needs a moderately structured treatment plan. The treatment plan will need to include psychological and rehabilitative components. Development of alternative coping strategies is important and the role and importance of pain medications as a coping strategy should be minimized. Long-acting time-contingent opioids are the drugs of choice with very limited reliance on breakthrough medications. On the other extreme of the continuum lies the high-risk patient with ongoing substance abuse issues, the patient in a drug-free recovery or the patient on methadone maintenance. These patients will require a highly structured plan including a signed treatment agreement (contract), frequent follow-up visits, concurrent enrollment in a 12-step plan or similar support program with an active sponsor, psychological support and regular urine and other laboratory testing. Other strategies include prescribing small quantities of drug, contingency of prescription renewal on clinic attendance and no early refills. It is recommended that clinic appointments be scheduled regularly ahead of time so the patient does not have to call to make an appointment. Preferably only one single pharmacy should be used and in extreme cases the prescription may be sent directly to the pharmacy. The treatment plan must be documented in detail in the treatment agreement, and the patient must give written consent. Finally, any opioid treatment strategy must include regular monitoring of analgesia, activities of daily living, adverse effects and aberrant drug behaviors.

If aberrant drug behaviors occur during the course of therapy, the patient’s risk for addiction must be evaluated carefully and the differential diagnosis for aberrant behavior must be considered to make an appropriate diagnosis. Furthermore, the physician must be armed with both proactive and reactive strategies to deal with aberrant behavior. Proactive strategies include clear communication with the patient and their family regarding reasonable expectations of therapy and acceptable and unacceptable behaviors as discussed above. Reactive strategies include increasing the frequency of visits and prescribing smaller quantities of medication, limiting medications to long-acting opioids with lower abuse potential and eliminating short-acting agents and making treatment contingent upon participation in the psychological and rehabilitative components of treatment.
Suggested Reading


DIAGNOSIS AND TREATMENT OF NEUROPATHIC PAIN

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INTRODUCTION

Neuropathic pain (NeP) is chronic pain initiated by nervous system lesions or dysfunction and maintained by a number of mechanisms. Neuropathic pain is common and accounts for 25% to 50% of all visits to pain clinics with an estimated prevalence of over 4 million [1]. The selection of therapy is difficult because neuropathic pain has a complex pathophysiology: the precise mechanisms are unknown and multiple mechanisms can coexist in individual patients. Similarly, different patients respond very differently to treatment. Physicians often need to resort to empirical treatment and sequential use of different pharmaceuticals and combinations of therapies [2]. This article will review the pathophysiology, diagnosis and treatment of neuropathic pain.

PATHOPHYSIOLOGY

Several cellular and molecular mechanisms operating over different periods of time are thought to be involved in the abnormal peripheral and central nervous system activity associated with NeP.

Ion Channels and demyelination

Nerve injury is reported to evoke spontaneous discharges from the cell bodies of myelinated fibers at the levels of the dorsal root ganglia, but not from the cell bodies of unmyelinated axons. The mechanism of the spontaneous activity is thought to be secondary to an increase in concentration of sodium channels in neuromas, dorsal root ganglion cells and areas of demyelination [3].

Pain is a frequent symptom of demyelinating disease such as multiple sclerosis [4]. Normal intact nerves transmit impulses through well-insulated channels. Following nerve injury, this insulation can be disrupted, and the impulses carried in one nerve fiber may be transmitted to a neighboring fiber. Ephatic communication or “cross-talk” has been demonstrated following stimulation of adjacent fibers in the same trunk [5].

Cytokines, enzymes and neuropeptides

There are also certain receptors that may accumulate that respond to cytokines and enzymes associated with inflammation. Receptors for inflammatory cytokines such as tumor necrosis factor α (TNF-α) can accumulate in injured sensory neurons and alter their function. Interleukins 1 and 6 and TNF-α are elevated in vasculitic neuropathy, chronic inflammatory demyelinating neuropathy, and noninflammatory chronic neuropathy. Cytokine levels also rise after nerve transection, and this elevation is correlated with allodynic behavior that may be linked to glutamate release and NMDA receptor activation [6].

Membrane-type 5 matrix metalloproteinase (MT5-MMP) has been implicated in injury-associated spinal cord remodeling and development of NeP. Sciatic nerve damage results in sprouting of A beta afferents from laminae III–VI and into lamina I of the dorsal
horn and in the development of mechanical allodynia (see discussion below). Neither sprouting nor allodynia occurs after nerve damage in mice lacking the gene for MT5-MMP [7].

Nerve injuries associated with the development of NeP alter the expression of neuropeptides and their receptors. Vanilloid receptor 1 (VR1) is expressed on peripheral terminals of A delta and C fibers. However, in rats with streptozotocin-induced diabetes, peripheral terminals of A beta fibers also express VR1. Substance P (SP) is normally released from the central terminals of A delta and C fibers to bind with neurokinin-1 (NK-1) receptors on nociceptive neurons in the dorsal horn. NK-1 mRNA expression in the mouse lumbar dorsal horn is increased after partial sciatic nerve ligation, and this rise is correlated with thermal hyperalgesia. These results have prompted the suggestion that nerve injury results in synthesis and tonic release of SP by A beta fibers, which initiates ongoing excitation of NK-1–expressing spinal nociceptive neurons [8].

**A beta Sprouting**

Peripheral nerve injury triggers central sprouting of myelinated afferents. The myelinated afferents located in deeper layers of the dorsal horn cells (laminae III and IV) sprouting superficially to reach superficial layers of the dorsal horn (laminae I and II). Therefore, tactile nonpainful stimuli that activate large myelinated afferents will in turn activate superficial layers of the dorsal horn in turn activating spinothalamic tract neurons which will result in a painful state (allodynia) [9].

**Sympathetic-Somatosensory Crosstalk**

Discharge of afferent fibers has been observed following stimulation of sympathetic nerve fibers in the same nerve trunk. Sympathetic communication with afferent neurons is hypothesized to be the result of an increase in alpha adrenergic receptors in damaged primary afferent axons. Crosstalk between sympathetic and somatosensory afferents can develop in neuromas and DRGs. Sympathetic axons are present in neuromas, and α-adrenoceptor–mediated excitatory coupling has been demonstrated in both neuromas and DRGs [10].

In addition to alterations in adrenergic receptor expression, a recent report indicated that nerve injury causes sprouting of sympathetic fibers that invade the DRG to form functional synapses. These sprouting fibers contain catecholamines, and it has been demonstrated that ectopic discharges may originate at the DRG by direct innervation from these sympathetic fibers that form basket like structures around large diameter cell bodies of the DRG [11].

**GABA Down-regulation**

Spinal inhibitory interneurons modulate the peripheral-to-central transmission of pain signals, thus “gating” ascending sensory information. γ-Aminobutyric acid (GABA) and glycine and their receptors are abundant in the superficial dorsal horn, but their levels are regulated by primary afferent input and change significantly after nerve injury. Sciatic nerve transection decreases the number of GABA-immunoreactive cells in dorsal horn laminae I–III, and this may “open the gate” to allow more excitatory signals from pain (or nonpain) pathways to reach the brain. Nerve damage also reduces expression of GABA_A receptor α2 subunit mRNA in DRG cells, and this may disrupt the normal presynaptic inhibition that modulates neurotransmitter release by these cells [12].
Glutamatergic Neurotransmission

Increased glutamatergic neurotransmission may also contribute to hyperexcitability and NeP. Repeated noxious stimulation leads to temporal summation of dorsal horn excitatory postsynaptic depolarizations, and this amplification is reduced by the NMDA receptor antagonist d-2-amino-5-phosphonovaleric acid (d-APV), suggesting mediation by an increase in glutamate release from primary afferents and subsequent binding to NMDA receptors. Intrathecal NMDA causes an increase in spontaneous activity of dorsal horn neurons that can be reversed by d-APV. Persistent inflammation that gives rise to hyperalgesia is also associated with up-regulation of metabotropic glutamate receptors in the dorsal horn.

Dorsal horn neurons express amino-3-hydroxy-5-methylisoxazol propionic acid (AMPA)/kainate-type glutamate receptors; these non-NMDA receptors are thought to be primarily involved in detecting and responding to innocuous stimuli, but AMPA/kainate-NMDA receptor interactions are involved in C-fiber wind-up and long-term potentiation in dorsal horn neurons.

Glutamatergic transmission is potentiated by neuropeptides. For example, thyrotropin-releasing hormone has a slow priming effect that enhances NMDA receptor–mediated nociceptive transmission in the dorsal horn. Peripheral interactions between NK1 and NMDA receptors may also potentiate pain. NK1 receptor activation is thought to potentiate glutamatergic transmission in the spinal cord via NMDA-independent mechanisms.

Protein kinase C (PKC) potentiates NMDA currents by reducing the magnesium block and increasing the probability of channel openings. An additional consequence of protein phosphorylation is tolerance to opioids, which may result from desensitization of the opioid receptor by G-protein kinase 3.

Glutamatergic neurotransmission, most notably that involving NMDA receptors, also results in significant damage-associated changes in the anatomy of the spinal cord. For example, sciatic nerve transection results in degeneration of spinal dorsal horn neurons, and this apoptosis can be prevented when the NMDA antagonist MK-801 is injected before transection and then continuously infused.

Nociceptive processing also involves the expression of immediate early genes, a process partially regulated by glutamate receptors. Activity-dependent stimulation of kinases such as extracellular signal-regulated protein kinase), the Ras cascade, and other transcriptional factors appears to be involved in inflammatory pain and NeP [13].

DIAGNOSIS

There is no one diagnostic test for the presence of neuropathic pain. No single symptom or sign is pathognomonic. The diagnosis should begin with a detailed description of the pain given by the patient. Neuropathic pain is described by a variety of terms such as burning, shooting, or lancinating and may be present without demonstrable physical findings. Several studies have evaluated the correlation between symptoms and the presence of NeP. Backonja et al demonstrated that NeP sensations are diverse, but three symptoms—numbness, tingling, and increased pain due to touch—appear to predominate [14]. These symptoms illustrate the negative (sensory deficit) as well as positive (paresthesia and
alldynia/hyperalgesia) phenomena that distinguish neuropathic from nociceptive pain. Rasmussen et al studied the symptoms and signs in patients with suspected neuropathic pain and found that brush-evoked pain was more frequent in NeP, high intensity of superficial ongoing pain and touch or cold provoked pain was associated with possible or definite NeP. The McGill Pain Questionnaire, and intensity of deep ongoing pain and paroxysms were similar in NeP and non NeP [15]. A study by Bouhassira compared symptoms associated with NeP and somatic pain. They found that burning, electric shocks, tingling, pins and needles, itching, and numbness occurred more frequently in NeP [16]. Bennett et al evaluated the ability of the Leeds Assessment of Neuropathic Symptoms and Signs pain scale (S-LANSS) to detect NeP. The S-LANSS is a 7 item questionnaire about the patient’s pain experience. A score of 12 or more suggests pain of predominantly neuropathic origin. The authors found that the S-LANSS is a valid and reliable self-report instrument for identifying neuropathic pain [17]. Because NeP is highly heterogenous, it has been suggested that there are subgroups that may respond differently to pharmacologic intervention [18]. The Neuropathic Pain Symptom Inventory is a specific self-questionnaire for the assessment of the different symptoms of neuropathic pain. The validation of this questionnaire suggests that it may be useful to detect differences in pharmacologic response to treatment [19].

A thorough neurologic examination is an essential part of the assessment of a patient with chronic pain and helps confirm the diagnosis of a neuropathic pain disorder. Allodynia is assessed to determine if the injury responds to static, dynamic, or thermal pressure. These assessments can be conducted through a light rub with a fingertip, cotton swab, or paintbrush (dynamic allodynia); by applying perpendicular pressure slowly with a cotton swab or pencil eraser (static allodynia); and with a warm or cold test tube or tuning fork (thermal allodynia). Hyperalgesia is diagnosed if the patient has an exaggerated response to single or multiple pinpricks. Summation (increasing pain to each repeated stimulus although each stimulus is the same) and after-sensation (exceptionally long perception of a stimulus after it has been administered) usually occur during neuropathic pain. The examination of motor elements is to detect both negative and positive signs. Negative signs include weakened muscles, lowered endurance, and hypotonia. Positive signs are increased muscle tone, tremor, dystonia, and dyskinesia. Patients also should be examined for coordination, ataxia, and apraxia. An examination of the motor system provides an important indication that the nervous system, not only the pain-transmitting fiber, is injured[20]. An examination of the autonomic nervous system should seek to determine if the area of pain has abnormally hot or cold skin temperature changes, if the skin color has changed, if abnormal sweating has occurred or if the skin is unusually dry, or if abnormal hair and nail growth is present[21]. Although all of these examinations are important, it should be emphasized that all successful diagnosis and treatment begins with the physician acknowledging the reality of the patient’s pain[20].

In general, there is no single diagnostic test for neuropathic pain. Diagnostic studies can help confirm diagnostic impressions or rule out underlying causes (eg, rheumatologic causes) and diagnostic imperatives (eg, metastases in the cancer patient with new back pain). Blood studies can help identify systemic illnesses (eg, acute herpes virus infection) associated with neuropathies. Magnetic resonance imaging (MRI) can identify structural lesions, such as tumors or infections in the spine or plexus[22].

Computed tomography (CT) is similar to MRI, except it is less sensitive to soft tissue lesions. Electromyography (EMG) and nerve conduction velocity (NCV) testing can help localize a
neuropathy (eg, Is it a root or plexus neuropathy?), grade its severity, and help categorize the pathophysiology (axonal vs demyelinating). Quantitative sensory testing (QST) assesses small-fiber function, and can show abnormalities consistent with neuropathic pain even when an EMG and NCV are normal. These studies have important limitations. First, they do not measure pain and a patient may have neuropathic pain and normal studies, or have abnormal studies with no pain. Second, an EMG and NCV assess only large nerve fibers, which have little involvement in pain [22].

**TREATMENT**

The management of neuropathic pain encompasses establishing a diagnosis, treating any underlying condition that may be causing the pain, providing symptomatic relief from pain and disability, and preventing recurrence. Symptomatic treatment should be offered when specific treatment directed at the underlying cause is not available or is ineffective in reducing pain; measures to reduce disability should be advised. Pain as a symptom of an underlying illness that cannot be cured should be treated as a chronic illness. This is consistent with over 90% of medicine in which medical doctors simply treat the symptom of illnesses without affecting the course of the underlying illness (e.g. hypertension, diabetes). It should be recognized that pain is a symptom with underlying mechanisms and neuranatomic pathways with treatments directed at decreasing pain as a symptom.

Based on thorough assessment of a patient with chronic pain, a clinician can develop a comprehensive management plan that may or may not emphasize pharmacologic therapy among other multimodal treatment approaches. It is best to use a multidisciplinary approach in presence of depression, anxiety, chronically dysfunctional or angry patient, or one with personality disorders. A multidisciplinary approach may include psychological interventions, physical therapies, or alternative therapies such as acupuncture. The important thing to stress to the patient is that treatment is often multimodal with no one superior treatment.

Since nonpharmacologic treatment is often not sufficient for patients with neuropathic pain, pharmacotherapy constitutes the primary clinical approach. Five medications have been approved by the FDA for treatment of neuropathic pain—specifically, for treatment of postherpetic neuralgia (PHN) (lidocaine patch 5%, gabapentin, and pregabalin) painful diabetic neuropathy (PDN) (duloxetine and pregabalin) and trigeminal neuralgia (carbamazepine). Recently, Qutenza was FDA approved for the treatment of PHN.

**Topical Agents**

In two double-blind, vehicle-controlled randomized clinical trials, lidocaine patch 5% provided statistically significantly greater pain relief to patients with PHN than did vehicle-control patches without lidocaine [23, 24]. On the basis of those studies, FDA approved lidocaine for treatment of PHN. Anecdotal evidence of a beneficial treatment in patients with other types of neuropathic pain have been published [25, 26]. A systematic review of topical capsaicin for the treatment of chronic pain showed moderate to poor efficacy [27].

Recently, the advent of transdermal capsaicin patch has added another method to treat a classic form of neuropathic pain, post-herpetic neuralgia. Qutenza is a TRPV1 channel agonist indicated for the management of neuropathic pain associated with postherpetic neuralgia (PHN). It contains 8% capsaicin (640 mcg/cm2) and each patch contains a total of 179 mg of capsaicin. Although there are no known contraindications, several precautions exist
due to the irritative properties. Avoidance of contact with eyes and mucous membranes is critical. Albeit modest, transient rises in blood pressure are not uncommon; hence, risks may exceed benefits in any situation in which hypertension should be avoided.

The mechanism of action is mediated through agonist stimulation on the transient receptor potential vanilloid 1 receptor (TRPV1), which is an ion channel-receptor complex expressed on nociceptive nerve fibers in the skin. Topical administration of capsaicin causes an initial enhanced stimulation of the TRPV1-expressing cutaneous nociceptors that may be associated with painful sensations. Pain relief is thought to be mediated by a reduction in TRPV1-expressing nociceptive nerve endings.

The efficacy of Qutenza, was established in two 12-week, doubleblind, randomized, dose-controlled, multicenter studies treating patients with PHN. In the first 12-week study, the Qutenza group demonstrated a greater reduction in pain compared to the Control group during the primary assessment at Week 8. The percent change in average pain from baseline to Week 8 was -18% (±2%) for the low-dose control and -29% (±2%) for Qutenza. In the second 12-week study the Qutenza group demonstrated a greater reduction in pain compared to the Control group during the primary assessment at Week 8. The percent change in average pain from baseline to Week 8 was -26% (±2%) for the low-dose control and -33% (±2%) for Qutenza [Qutenza prescribing information].

**Antiepileptic Drugs**

The use of antiepileptic drugs (AED) to treat neuropathic pain is based upon a number of similarities between the pathophysiologic and biochemical mechanisms observed in neuropathic pain and epilepsy—particularly between “wind-up” in dorsal horn neurons and the “kindling” of hippocampal neurons in epilepsy. Although their precise mechanisms vary, AEDs generally enhance inhibitory neurotransmission, reduce excitatory neurotransmission, and regulate cation channel conductance [28]. There is also some evidence that AEDs have neuroprotective effects; however, an effect of early use of AEDs in preventing NeP has yet to be demonstrated [29].

Gabapentin is the first anticonvulsant drug to receive FDA approval for the treatment of a neuropathic pain syndrome (postherpetic neuralgia). The exact mechanism of action is unknown but thought to bind to the α2δ subunit of voltage-gated calcium channels resulting in the inhibition of glutamate release in the spinal dorsal horn [30]. Gabapentin has been shown to be clinically effective in a variety of neuropathic pain syndromes [31-33]. Eight double-blind, placebo-controlled, randomized clinical trials of gabapentin for chronic pain found that, at daily dosages up to 3600 mg, gabapentin significantly reduced pain compared with placebo in patients with PHN, painful diabetic neuropathy (PDN), mixed neuropathic pain syndromes, among other neuropathic disorders. On the basis of two large randomized trials, FDA approved gabapentin for treatment of PHN [32, 33]. These two studies that led to the FDA approval for postherpetic neuralgia targeted daily doses ranging from 1800 mg/day to 3600 mg/day [32, 33]. Efficacy was demonstrated over the range of 1800-3600 mg/day; however, additional benefit of using doses greater than 1800 mg/day was not demonstrated. Based on these studies, gabapentin is approved for the treatment of postherpetic neuralgia at doses of up to 1800mg/day. Backonja and colleagues reported the results of a randomized, double-blind, placebo-controlled clinical trial of the anticonvulsant gabapentin for the treatment of pain associated with diabetic peripheral neuropathy. Patients received 8 weeks of treatment with
either gabapentin, titrated to 3,600 mg/day or maximum tolerated dosage, or a matching placebo. Patients who received gabapentin had significantly less pain at weeks 2 through 8 than did those who received placebo [31]. Caraceni and colleagues reported the results of a randomized controlled trial from the gabapentin cancer pain study group. Cancer patients with neuropathic pain partially controlled with systemic opioids received either gabapentin 600-1800 mg/day or placebo. Patients who received gabapentin showed significantly lower pain scores [34].

The efficacy of pregabalin in managing PHN was shown in two 8-week, double-blind, placebo-controlled trials [35, 36]. Pregabalin at doses of up to 600 mg/day showed a significant reduction in mean pain scores beginning at day 2 of treatment and continuing through the study end. There were also significant reductions in sleep interference scores in the pregabalin group. The efficacy of pregabalin has also been demonstrated in PDN [37, 38]. Significant effects on pain and sleep was demonstrated in doses ranging from 300-600 mg/day.

There are many reports on the efficacy of other AEDs in the treatment of neuropathic pain; however, only two have been subjected to rigorous double-blind, placebo-controlled multicenter trials. Topiramate has been evaluated in three double-blind placebo-controlled trials in PDN. These studies failed to show a reduction in pain scores [39]. A follow-up study using slightly different methods demonstrated a significant effect of topiramate on PDN. This follow-up study used patients with higher baseline pain scores and different pain intensity assessments [40]. Dogra and colleagues reported the results of a multicenter randomized, placebo-controlled study of oxcarbazepine in PDN. Patients received oxcarbazepine 300-1800 mg/day or placebo over 16 weeks. Oxcarbazepine patients experienced a significantly larger decrease in the average change in pain score from baseline compared to placebo [41]. Carbamazepine has a well-established beneficial effect in trigeminal neuralgia, and it is approved by the FDA for the treatment of this syndrome. Based on the results of the clinical trials of anticonvulsants in chronic neuropathic pain, carbamazepine can be recommended for patients who have not responded to an adequate trial of gabapentin when treatment with an anticonvulsant is sought [42].

Antidepressants

Many controlled clinical trials and meta-analyses have demonstrated that TCAs (eg, imipramine, amitriptyline, desipramine, nortriptyline, clomipramine) can significantly reduce the pain of diabetic neuropathy and PHN [43-45]. Some, but not all, selective serotonin reuptake inhibitors (SSRIs) have also been shown to be effective for neuropathic pain [46]. Paroxetine and citalopram (slightly) have shown benefit for diabetic neuropathy, while fluoxetine has proved to be no more effective than placebo [47]. In general the SSRIs are felt to be, at best, inconsistently effective for neuropathic pain. The FDA approved duloxetine hydrochloride for the management of pain associated with diabetic neuropathy in September, 2004. In a 12-week study, patients with diabetic neuropathic pain and without comorbid depression were randomized to treatment with duloxetine 60 mg qd, duloxetine 60 mg bid, or placebo. Both dosages of duloxetine were superior to placebo in reducing pain as measured by the weekly 24-hour average pain severity score, with statistically significant separation from placebo occurring at week 1 and continuing throughout the 12-week period. Duloxetine was also superior to placebo for almost all secondary outcomes (eg, Brief Pain Inventory severity scores), with no significant differences between the two dosages [48]. In a 6 week, double-blinded, placebo-controlled trial with venlafaxine in PDN, it was demonstrated that
venlafaxine significantly reduced pain; however, onset was delayed at 6 weeks. The effective
dose was 150-225 mg/day [49].

**Opioids**

There are numerous studies supporting the efficacy of the opioids in the treatment of
neuropathic pain. Dellemijn and Vanneste demonstrated that fentanyl was beneficial in a
variety of neuropathic pain syndromes, which included PHN, radiculopathy, posttraumatic
nerve pain, and other types of pain. Fentanyl relieved pain intensity and unpleasantness
equally, but a comparison drug, diazepam, and placebo did not decrease either pain
measurement [50]. In a study by Rowbotham and colleagues in PHN, IV morphine
administered with IV lidocaine reduced pain intensity. Allodynia disappeared in patients who
reported pain relief [51].

Watson and Babul demonstrated that controlled-release (CR) oxycodone significantly
\( P=0.0001 \) decreased pain from PHN without causing serious adverse effects [52]. A small
\( N=12 \) double-blind crossover study conducted by Huse et al found that morphine, but not
placebo, produced a significant \( P<0.01 \) reduction in phantom limb pain. A pain reduction of
more than 50% occurred in 42% of patients receiving morphine, which may also influence
cortical reorganization [53].

In a study of 131 patients with diabetic neuropathy, tramadol was significantly more
effective \( P<0.001 \) than placebo in treating pain. Patients in the tramadol group also scored
significantly better in physical \( P=0.02 \) and social functioning \( P=0.04 \) [54]. A follow-up
study demonstrated long-term efficacy [55].

**Miscellaneous Drugs**

Several studies have demonstrated the efficacy of the cannabinoids in the treatment of
neuropathic pain. The cannabinoids are thought to modulate pain through the CB1 receptor.
In a study using patients with chronic neuropathic pain (21 subjects), it was demonstrated that
a synthetic cannabinoid was effective in reducing pain compared to placebo [56]. Berman et
al studied the effect of two cannabis extracts on central neuropathic pain from brachial plexus
avulsion. Although there was no effect on the primary efficacy endpoint of mean daily pain
score, there was a significant effect on the SF-MPQ pain rating index and sleep scores [57].

In PDN patients, it has been suggested that the deficiency of acetyl-carnitine leads to
leads to ongoing neuropathic pain due to perturbations in Na/K-ATPase, myoinositol, nitric
oxide, prostaglandins, and lipid peroxidation. In two studies amounting to 1257 patients, it
was demonstrated that acetyl-carnitine is efficacious in alleviating symptoms, particularly
pain, and improves nerve fiber regeneration and vibration perception in patients with
established diabetic neuropathy [58].
REFERENCES:

CLINICAL DIAGNOSTIC CRITERIA
FOR CRPS

AND A REVIEW ARTICLE:

Proposed New Diagnostic Criteria for Complex Regional
Pain Syndrome
Clinical diagnostic criteria for CRPS

**General definition of the syndrome:** CRPS describes an array of painful conditions that are characterized by a continuing (spontaneous and/or evoked) regional pain that is seemingly disproportionate in time or degree to the usual course of any known trauma or other lesion. The pain is regional (not in a specific nerve territory or dermatome) and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor, and/or trophic findings. The syndrome shows variable progression over time.

**To make the clinical diagnosis, the following criteria must be met:**

1. Continuing pain, which is disproportionate to any inciting event
2. **Must report at least one symptom in three of the four following categories:**
   - **Sensory:** Reports of hyperesthesia and/or allodynia
   - **Vasomotor:** Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
   - **Sudomotor/Edema:** Reports of edema and/or sweating changes and/or sweating asymmetry
   - **Motor/Trophic:** Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
3. **Must display at least one sign at time of evaluation in two or more of the following categories:**
   - **Sensory:** Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement)
   - **Vasomotor:** Evidence of temperature asymmetry (>1°C) and/or skin color changes and/or asymmetry
   - **Sudomotor/Edema:** Evidence of edema and/or sweating changes and/or sweating asymmetry
   - **Motor/Trophic:** Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
4. There is no other diagnosis that better explains the signs and symptoms

**For research purposes,** diagnostic decision rule should be at least one symptom in all four symptom categories and at least one sign (observed at evaluation) in two or more sign categories.

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Proposed New Diagnostic Criteria for Complex Regional Pain Syndrome (p 326-331)
R. Norman Harden, Stephen Bruehl, Michael Stanton-Hicks, Peter R. Wilson
Published Online: Feb 12 2007
Volume 8 Issue 4 Pain Medicine
This topical update reports recent progress in the international effort to develop a more accurate and valid diagnostic criteria for complex regional pain syndrome (CRPS). The diagnostic entity of CRPS (published in the International Association for the Study of Pain’s Taxonomy monograph in 1994; International Association for the Study of Pain [IASP]) was intended to be descriptive, general, and not imply etiopathology, and had the potential to lead to improved clinical communication and greater generalizability across research samples. Unfortunately, realization of this potential has been limited by the fact that these criteria were based solely on consensus and utilization of the criteria in the literature has been sporadic at best. As a consequence, the full potential benefits of the IASP criteria have not been realized. Consensus-derived criteria that are not subsequently validated may lead to over- or underdiagnosis, and will reduce the ability to provide timely and optimal treatment. Results of validation studies to date suggest that the IASP/CRPS diagnostic criteria are adequately sensitive; however, both internal and external validation research suggests that utilization of these criteria causes problems of overdiagnosis due to poor specificity. This update summarizes the latest international consensus group’s action in Budapest, Hungary to approve and codify empirically validated, statistically derived revisions of the IASP criteria for CRPS.

Key Words.
Complex Regional Pain Syndrome; Reflex Sympathetic Dystrophy; Causalgia; Diagnostic Criteria

Introduction
Complex regional pain syndrome (CRPS) has been known by many names, but most commonly as reflex sympathetic dystrophy and causalgia (as attributed to Evans and Mitchell, respectively) [1,2]. In the past, it was diagnosed using a variety of nonstandardized and idiosyncratic diagnostic systems (e.g., [3–6], each of which was derived solely from the authors’ clinical experiences and none of which achieved wide acceptance. After much debate in the literature and at scientific meetings, the name was ultimately changed to complex regional pain syndrome (CRPS) at a consensus workshop in Orlando, Florida, in 1994 [7,8], with the new name and diagnostic criteria codified by the International Association for the Study of Pain (IASP) task force on taxonomy (Table 1) [9]. The new diagnostic entity of CRPS was intended to be descriptive, general, and not imply any etiopathology (including any direct role for the sympathetic nervous system). This pivotal effort finally provided an officially endorsed set of standardized diagnostic criteria that had the potential to lead to
improved clinical communication and greater generalizability across research samples [7]. However, realization of this potential has been somewhat limited by the fact that these criteria were based solely on consensus, utilization of the criteria in the literature has been sporadic at best [10], and certain influential groups have resisted the change (e.g., personal injury lawyers, who may benefit by a “looser” criteria, and some ill informed patient advocacy organizations that fear a “tighter” criteria may cause many previously diagnosed patients to be thrown into diagnostic limbo: see discussion of CRPS—not otherwise specified (NOS) below). As a consequence, the full benefits of the common, consensus-defined IASP criteria have not been completely realized.

Methods

A “closed” workshop (by invitation only) was held in Budapest, Hungary, in the fall of 2003. One day was devoted to a discussion of the diagnostic criteria with a stated goal of “to review the terminology of complex regional pain syndromes in light of experience gained since its introduction as component of the taxonomy of chronic pain.” There were 35 professionals attending from seven countries (see Table 2 for list of attendees). The diagnostic criteria workshop loosely followed a “Dahlem” think tank type of format with didactic presentations followed by breakout working groups, full group discussion, a second round of breakout sessions, and a final full session. Formal recommendations were made to endorse the recommended research criteria that had been previously formulated by empiric research [11,12]. This was followed by a day to discuss the treatment of CRPS and half a day of presentations to an open audience. A book was published concerning diagnostic and therapeutic issues by workshop attendees on the basis of these recommendations [13]. The recommendations of this panel have been formally submitted to the IASP’s task force on taxonomy for consideration in the third edition of the classification of chronic pain: descriptions of chronic pain syndromes and definition of pain terms (published by IASP Press).

There is controversy about the value of the consensus process in this setting. There has been an almost complete absence of evidence-based information about this condition since it was newly defined. It is therefore not possible to apply the usual scientific tools to the problem of diagnosis and therapy. The consensus process has been widely accepted in medicine, and is the subject of study by groups such as the National Institutes of Health (see http://www.consensus.nih.gov/about/references.htm). For example, experience has been gained in developing diagnostic criteria for headache and psychiatric disorders. These highlight the necessity of validating and modifying initial consensus-based criteria in the light of systematic validation research [14]. Consensus-derived criteria that are not subsequently validated may lead to over- or underdiagnosis, and will reduce the ability to provide timely and optimal treatment. This review summarizes the latest international consensus group’s action in Budapest, Hungary, to approve and codify empirically validated revisions of the IASP criteria for CRPS [15].

Results of validation studies to date suggest that the IASP/CRPS diagnostic criteria are adequately sensitive (i.e., rarely miss a case of actual CRPS). However, both internal and external validation research suggests that using these criteria causes problems of overdiagnosis due to poor

<table>
<thead>
<tr>
<th>Table 1</th>
<th>IASP diagnostic criteria for complex regional pain syndrome (CRPS)* (adapted from [9])</th>
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<tbody>
<tr>
<td>1.</td>
<td>The presence of an initiating noxious event, or a cause of immobilization†</td>
</tr>
<tr>
<td>2.</td>
<td>Continuing pain, allodynia, or hyperalgesia in which the pain is disproportionate to any known inciting event.</td>
</tr>
<tr>
<td>3.</td>
<td>Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of pain (can be sign or symptom)</td>
</tr>
<tr>
<td>4.</td>
<td>This diagnosis is excluded by the existence of other conditions that would otherwise account for the degree of pain and dysfunction</td>
</tr>
</tbody>
</table>

* If seen without “major nerve damage” diagnosis CRPS I. if seen in the presence of “major nerve damage” diagnosis CRPS II. † Not required for diagnosis; 5-10% of patients will not have this.
specificity [11,12,16]. The current IASP criteria implicitly assume that signs and symptoms of vasomotor sudomotor, and edema-related changes provide redundant diagnostic information; that is, the presence of any one of these is sufficient to meet criterion 3. This combination of multiple distinct elements of the syndrome into a single diagnostic criterion in the current IASP system appears to be one element compromising specificity [11,15]. Wording of the current IASP criteria that permits diagnosis based solely on patient-reported historical symptoms may also contribute to overdiagnosis. An additional weakness of the current criteria is their failure to include motor/trophic signs and symptoms, which can lead to important information being ignored that may discriminate CRPS from other syndromes [16–18].

The conclusions above are supported by the results of a factor analysis that was conducted in a series of 123 CRPS patients. These results indicated that signs and symptoms of CRPS actually clustered into four statistically distinct subgroups [11]. The first of these subgroups is a unique set of signs and symptoms indicating abnormalities in pain processing (e.g., allodynia, hyperalgesia). Skin

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Workshop attendees, Budapest, Hungary, fall 2003</th>
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<tbody>
<tr>
<td>Ralf Baron, MD Kiel, Germany</td>
<td>David Nix, MD Tel-Aviv Sourasky Medical Center Tel-Aviv, Israel</td>
</tr>
<tr>
<td>Frank Birklund, MD Neurologische Universitätsklinik Mainz Mainz, Germany</td>
<td>Anne Louise Oaklander, MD, PhD Massachusetts General Hospital MA, USA</td>
</tr>
<tr>
<td>Helmut Blumberg, MD Freiburg, Germany</td>
<td>Gunnar Olsson, MD, PhD Docent Pain Treatment Solothurn, Switzerland</td>
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<tr>
<td>Stephen Bruhl, PhD Vandenhoff University TN, USA</td>
<td>Joshua Prager, MD California Pain Management Center CA, USA</td>
</tr>
<tr>
<td>Allen W. Burton, MD MD Anderson Cancer Center TX, USA</td>
<td>Gabor Racz, MD Texas Tech University Health Sciences TX, USA</td>
</tr>
<tr>
<td>Peter D. Drummond, PhD Murdoch University Perth, Australia</td>
<td>Prithvi Raj MD Texas Tech University Health Sciences TX, USA</td>
</tr>
<tr>
<td>Jan H.B. Geertzen, MD, PhD Center for Rehabilitation Groningen, The Netherlands</td>
<td>Sreewasa Raja, MD Johns Hopkins University School of Medicine MD, USA</td>
</tr>
<tr>
<td>Heinz-Joachim Haehl, MD Christian-Albrechts University Kiel, Germany</td>
<td>Richard L. Rauck, MD Pain Consultants P.A. Kiel, Germany</td>
</tr>
<tr>
<td>R. Norman Harden, MD Rehabilitation Institute of Chicago IL, USA</td>
<td>Olivier Rommel, MD Laboratory for Schmertztherapye Bad Wildbad, Germany</td>
</tr>
<tr>
<td>Mark Hendrickson, MD Cleveland Clinic Foundation OH, USA</td>
<td>Robert J. Schwartzman, MD Drexel University College of Medicine OH, USA</td>
</tr>
<tr>
<td>Thomas I. Janicki, MD Case Western Reserve University OH, USA</td>
<td>Lijodie Van der Leen, MD St. Antonius Hospital OH, USA</td>
</tr>
<tr>
<td>Wilfred Janig, MD</td>
<td>Bob J. Van Holten, MD Nieuweweg, The Netherlands</td>
</tr>
<tr>
<td>Christian-Albrechts Universitat</td>
<td>Leiden University Medical Center Leiden, The Netherlands</td>
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<tr>
<td>Kiel, Germany</td>
<td>Leiden, The Netherlands</td>
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<tr>
<td>Marius A. Kentler, MD, PhD Martin Hospital Groningen, The Netherlands</td>
<td>Gunnar L. Wasner, MD Klinik Fuer Neurologue Kiel, Germany</td>
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<tr>
<td>Timothy R. Lubenow, MD Rush Pain Center IL, USA</td>
<td>Robert T. Wilder, MD Mayo Clinic IL, USA</td>
</tr>
<tr>
<td>Harold Merskey, DM FRCP University of Western Ontario Ontario, Canada</td>
<td>Peter R. Wilson, MB, BS Mayo Clinic MN, USA</td>
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</table>

The conclusions above are supported by the results of a factor analysis that was conducted in a series of 123 CRPS patients. These results indicated that signs and symptoms of CRPS actually clustered into four statistically distinct subgroups [11]. The first of these subgroups is a unique set of signs and symptoms indicating abnormalities in pain processing (e.g., allodynia, hyperalgesia). Skin
color and temperature changes, which are indicative of vasomotor dysfunction, characterize the second subgroup. Edema and sudomotor dysfunction (e.g., sweating changes) combined to form a third unique subgroup. The finding that vasomotor signs and symptoms were statistically distinct from those reflecting sudomotor changes/edema is in contrast to the IASP criteria, which treat all three of these as diagnostically equivalent. A fourth and final separate subgroup was identified that included motor and trophic signs and symptoms. Numerous studies have described various signs of motor dysfunction (e.g., dystonia, tremor) as important characteristics of this disorder, and trophic changes have frequently been mentioned in historical clinical descriptions [6,17,19]. The absence of these features from the current IASP criteria is notable, especially given factor analytic findings that this subgroup of signs and symptoms does not overlap significantly with the other characteristics of CRPS used in the IASP criteria. External validity, which addresses the ability of the diagnostic criteria to distinguish CRPS patients from those with other types of pain conditions (specificity), is obviously an important issue.

In the absence of a definitive pathophysiology of CRPS and thus the absence of a definitive objective test to serve as a “gold standard,” providing evidence for external validity of a diagnostic criteria is challenging [12]. However, the upper limit on external validity can be evaluated by using the original criteria themselves as a reference point [12,16]. In this methodology, the researcher must employ a strict application of the IASP/CRPS criteria in order to distinguish a CRPS patient group from a comparison group of non-CRPS neuropathic pain patients who are defined by independent diagnostic information (e.g., chronic diabetes with ascending symmetrical pain, corroborated by electrodiagnostic studies). Existing criteria and modifications to these criteria can then be evaluated with regard to their ability to distinguish between these two groups based on patterns of signs and symptoms. While a defined disorder such as diabetic neuropathy is not likely to present a differential diagnostic challenge in actual clinical practice, use of such disorders for testing the discriminative utility of CRPS diagnostic signs and symptoms provides a model for examining external validity issues.

This model was used to test the accuracy of the IASP/CRPS criteria for discriminating between 117 patients meeting IASP criteria and 43 neuropathic pain patients with established non-CRPS etiology. The IASP/CRPS criteria and decision rules (e.g., “evidence at some time” of edema or color changes or sweating changes that satisfy criterion 3) did discriminate significantly between the CRPS and non-CRPS groups. However, closer examination of the results indicated that while diagnostic sensitivity (i.e., the ability to detect the disorder when it is present) was quite high (0.98), specificity (i.e., minimizing falsepositive diagnoses) was poor (0.36); thus a positive diagnosis of CRPS was likely to be correct in as few as 40% of cases [12].

For clinical purposes, sensitivity is extremely important. On the other hand, specificity is critical in the selection of research samples. High sensitivity at the expense of specificity in a diagnostic criteria may lead to overdiagnosis and, ultimately, unnecessary, ineffective, and potentially invasive treatments. Such diagnostic criteria also have the significant downside of identifying pathophysiologically heterogeneous groups for research, potentially contributing to negative results in clinical trials. Such overdiagnosis (due to poor specificity) must be balanced with the equally undesirable consequences of failing to identify clinically relevant syndromes and treat patients inadequately (due to poor sensitivity).

**Statistically Derived Revision of CRPS Criteria**

A set of modified diagnostic criteria for further exploration was developed based on results of validation studies [11,12]. These modified criteria assessed CRPS characteristics within each of the four statistically derived factors described above. Given evidence from Galer et al. [16] and Harden et al. [11] that objective signs on examination and patient-reported symptoms both provide useful and nonidentical information, the modified criteria required the presence of signs and symptoms of CRPS...
for diagnosis [11,16]. A study of these modified criteria testing their ability to discriminate between the CRPS and non-CRPS neuropathic pain groups indicated that they could increase diagnostic accuracy [12]. Results indicated that a decision rule requiring two of four sign categories and three of four symptom categories for a diagnosis to be made resulted in a sensitivity of 0.85 and a specificity of 0.69 (Table 3). This decision rule represented a good compromise between identifying as many patients as possible in the clinical context while substantially reducing the high level of false-positive diagnoses associated with current IASP criteria. This decision rule was therefore adopted in a set of Clinical Diagnostic Criteria endorsed by the Budapest group (summarized in Table 3).

<table>
<thead>
<tr>
<th>Table 3  Proposed clinical diagnostic criteria for CRPS</th>
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<tr>
<td>General definitions of the syndrome:</td>
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<td>CRPS describes an array of painful conditions that are characterized by continuing (spontaneous and/or evoked) regional pain that is seemingly disproportionate in time or degree to the usual course of any known trauma or other lesion. The pain is regional (not in a specific nerve territory or dermatome) and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor, and/or trophic findings. The syndrome shows variable progression over time.</td>
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<td>2. Must report at least one symptom in three of the four following categories:</td>
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<td>Sensory: Reports of hyperesthesia and/or allodynia</td>
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<td>Vasomotor: Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry</td>
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<td>Motor/Trophic: Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nails, skin)</td>
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<td>3. Must display at least one sign at time of evaluation in two or more of the following categories:</td>
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<td>Sensory: Evidence of hyperesthesia (to pinprick) and/or allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement)</td>
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<td>Vasomotor: Evidence of temperature asymmetry (&gt;1°C) and/or skin color changes and/or asymmetry</td>
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<td>Motor/Trophic: Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nails, skin)</td>
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<tr>
<td>4. There is no other diagnosis that better explains the signs and symptoms</td>
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<tr>
<th>Table 4  Summary of decision rules considered (modified from [12])</th>
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<tr>
<td>Criteria/Decision Rules for Proposed Criteria</td>
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<tr>
<td>2+ sign categories &amp; 2+ symptom categories</td>
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<tr>
<td>2+ sign categories &amp; 3+ symptom categories</td>
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<tr>
<td>2+ sign categories &amp; 4 symptom categories</td>
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<td>3+ sign categories &amp; 4 symptom categories</td>
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Both sensitivity and specificity can be strongly influenced by the decision rules employed [12], and optimization of decision rules depends on the purpose for which they are intended, such as identifying stringent research samples (minimizing false positives) vs clinically identifying as many CRPS patients as possible (minimizing false negatives). The proposed clinical diagnostic criteria described above reflected an improvement over current IASP criteria for clinical purposes, but still suffered from less than optimal specificity for use in the research context. Tests of the modified CRPS criteria above indicated that modifying the decision rules to require that two of four sign categories and four of four symptom categories be positive for diagnosis to be made in a research setting resulted in a sensitivity of 0.70 and a specificity of 0.94. Of all the permutations tested, this decision rule resulted in the greatest probability of accurate diagnosis for both CRPS and non-CRPS patients (approximately 80% and 90% accuracy, respectively; see Table 4 for a summary of decision rules considered) [12]. This high level of specificity was considered desirable in the research context by the Budapest
Thus, the proposed revision to the CRPS criteria endorsed by the Budapest group resulted in two similar sets of diagnostic criteria, differing only in the decision rules employed to optimize their use for clinical vs research purposes. Current distinctions between CRPS type I and CRPS type II subtypes, reflecting, respectively, the absence and presence of evidence of peripheral nerve injury, were retained by consensus despite ongoing questions as to whether such distinctions have clinical utility. The consensus group also was concerned about the approximately 15% of patients previously diagnosed with CRPS who would now be without a diagnosis. A third diagnostic subtype called CRPS-NOS was recommended that would capture those patients who did not fully meet the new clinical criteria, but whose signs and symptoms could not better be explained by another diagnosis [15]. In other words, those patients who have fewer than three symptom or two sign categories, or who were not showing a sign at the time of the examination, but had exhibited this previously, and whose signs and symptoms were felt to be best explained by CRPS, would receive a diagnosis of CRPS-NOS.

Conclusions and Clinical Implications
The IASP diagnostic criteria were designed to provide a standardized, common methodology for making decisions as to whether unidentified pain conditions represent CRPS or not. Treatment for two distinct conditions should differ, and application of inappropriate (and possibly expensive and/ or dangerous) treatments due to misdiagnosis can contribute to excessive medical costs, or worse, may delay the appropriate treatment. Thus, the statistically derived revisions of CRPS diagnostic criteria endorsed by the Budapest consensus group may impact positively on problems of medical overutilization and patient quality of life. These revisions should also assist in identifying more homogeneous research samples to evaluate and improve therapeutic options [15,20]. A test of the modified research diagnostic criteria indicates that it is possible to reduce the rate of overdiagnosis dramatically, although such changes modestly diminish diagnostic sensitivity as well [12]. The relative merits of enhanced specificity at the expense of diagnostic sensitivity were discussed extensively by the consensus group, with the result being that two similar sets of criteria were adopted specifically for use in clinical vs research settings, differing only in the decision rules employed (summarized in Table 1). These new criteria will now, of course, need to be further validated. The closed consensus workshop in Budapest adopted and codified the revised criteria described above (Table 3), and they are being proposed to the Committee for Classification of Chronic Pain of the IASP for inclusion in future revisions of their formal taxonomy and diagnostic criteria for pain states.

REFERENCES
DIAGNOSIS AND TREATMENT OF CHRONIC HEADACHE

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&
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University of California San Diego
DIAGNOSIS AND TREATMENT OF CHRONIC HEADACHE

Benjamin Atwater, M.D. and Erin Lawson, M.D.

University of California San Diego

Content Outline:

✓ Migraine
  o Diagnosis
  o Triggers
  o Acute Treatment
  o Preventative Management

✓ Tension-Type Headache
  o Diagnosis
  o Acute Treatment
  o Preventative Management

✓ Cluster Headache and Chronic Paroxysmal Hemicrania
  o Clinical features
  o Acute Treatment
  o Preventative Management

✓ Chronic Daily Headache
  o Diagnosis
  o Etiology
  o Preventative Management

✓ Cervicogenic Headache
  o Clinical features
  o Treatment

✓ Other Miscellaneous Headaches including Organic Headaches
Migraine

- Epidemiology: 18% of women, 6% of men, 4% of children

- Clinical features:
  - At least five attacks with the following features:
    - Duration: 4-72 hours
    - Location: unilateral
    - Character: pulsating
    - Intensity: moderate to severe, aggravated by exertion
    - Associated symptoms: nausea or vomiting, photophobia, phonophobia
    - Neck pain reported by 75% of migraine patients: stiffness or tightness

- Classic Migraine: Visual aura precedes headache
- Common Migraine: No aura associated with headache
- Chronic migraine: headache on more than 15 days per month in patients with migraine not attributed to another disorder. Chronic migraine is difficult to treat and requires a multidisciplinary approach.

Trigger factors in Migraine:

Psychological
- Stress
- Tension
- Anxiety
- Letdown
- Lack of sleep

Neurological and Medical
- Oral contraceptives
- Obstructive Sleep Apnea
- Cerebral Venous Sinus Thrombosis
- Bright lights or glare
- Odors, Changes in sleep patterns, Hormonal changes (menstruation)
- Changes in weather or temperature

Physical
- Exercise
- Fatigue
- Sexual activity
- High altitude

Dietary
- Missed or delayed meals
- Certain foods especially containing tyramine or caffeine
- Alcohol
Migraine pathophysiology
Central sensitization with activation (sensitization) of peripheral C fibers into the trigeminal system. C fibers are activated by mechanical, chemical, or thermal triggers. Activated C fibers release CGRP, substance P, glutamate. Histamine and prostaglandin E2 levels are increased by this sterile neurogenic inflammation. Trigeminovascular input to 2° neurons in trigeminocervical complex. Neurons in the trigeminocervical complex are the major relay neurons for nociceptive afferent input from the meninges and cervical structures. Modulation by trigeminal-autonomic reflex
Trigeminocervical complex

Somatotopic communication between spinal nucleus of V and upper cervical roots

Spinal trigeminal nucleus at C1 level
Work up for chronic migraine:
- Evaluate for lifestyle triggers (OCPs?)
- C spine MRI to R/O cervicogenic HA
- MR Venography to R/O sinus thrombosis
- If patient is obese, consider spinal tap for pseudotumor
- Sleep study for OSA
- Echocardiogram with bubble study for PFO

Patent Foramen Ovale in Migraine:
There is an increased incidence of PFO in chronic migraine sufferers. Migraine is present in about 13% to 50% of people with PFO as compared to approximately 4% of the general population. [Migraine with aura is more prevalent in subjects with PFO and PFO is more prevalent in subjects who have migraine with aura. However, it is unclear if there is a causal relationship or simply a co-existence of these two conditions.

It is prudent to evaluate chronic migraine patients with echocardiogram with bubble study to assess for PFO. Chronic anticoagulation with ASA may be considered for patients with known PFO.

Acute Therapy for Migraine

Abortive therapy
Abortive agents should be taken as soon as possible at the beginning of a migraine attack and should NOT be taken on a daily basis.

NSAIDs or combinations (diclofenac potassium in a sachet)

Triptans: Serotonin 5-HT1B/1D–receptor agonists
- Sumatriptan, zolmitriptan, naratriptan, rizatriptan, almotriptan, frovatriptan, eletriptan
- Sumatriptan is available by iontophoretic patch (Zelrix from NuPathe) or by needle-free injections (Sumavel DosePro by Zogenix)
- Triptans cause vasoconstriction and are not safe for patients with ischemic heart disease, hypertension, myocardial infarction, or Prinzmetal angina. Triptans should never be administered concomitantly with ergotamine medications or MAOIs.

Ergot Derivatives: ergotamine and dihydroergotamine (DHE): nasal spray or parenteral administration.
- Intravenous administration for treatment of status migrainous or other intractable headaches.
- Potent vasoconstrictors; do not use in patients with unstable hypertension ischemic heart disease, history of MI, impaired renal and hepatic function, infection, and pregnancy.

CGRP antagonists: (BIBN 4096 BS @ 2.5 mg)
- CGRP is released from the trigeminal nerves appears to be involved in the pathophysiology of migraine. CGRP is a potent cerebral and dural vessel dilator which is released from trigeminal ganglia. CGRP causes release of inflammatory agents from
meningeal mast cells and is involved in the transmission of pain producing stimuli from intracranial vessels to the central nervous system. Serum levels of CGRP are elevated in patients with cluster headaches and Migraine. BIBN 4096 BS 2.5 mg infusion has been proven effective for acute treatment of migraine (response rate of 66 percent, as compared with 27 percent for placebo P=0.001). The most common side effect reported was paresthesia.

**Opioids:**

Appropriate for use in patients with contraindications to the other abortive. Avoid in patients at high risk for abuse, also advise of risk of rebound headaches

**Preventive Therapy for Migraine**

**Behavioral:**
- Maintain regular sleep pattern
- Maintain regular meal pattern
- Low tyramine and low caffeine diet
- Biofeedback
- Physical Therapy
- Stress management therapy
- Relaxation training
- Psychologic and/or psychiatric consultations

**Medications**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE</th>
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<tbody>
<tr>
<td>β-Adrenergic–receptor antagonists</td>
<td></td>
</tr>
<tr>
<td>Propranolol (non-selective)</td>
<td>80 – 240 mg daily</td>
</tr>
<tr>
<td>Metoprolol (cardioselective)</td>
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<tr>
<td>Calcium channel blockers</td>
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<tr>
<td>Verapamil</td>
<td>120–360 mg daily</td>
</tr>
<tr>
<td>Flunarizine</td>
<td>5–15 mg daily</td>
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<tr>
<td>Antidepressants (TCAs)</td>
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<tr>
<td>Amitriptyline</td>
<td>25–75 mg at bedtime</td>
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<tr>
<td>Nortriptyline</td>
<td>25 – 100 mg at bedtime</td>
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<tr>
<td>Anticonvulsants</td>
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<tr>
<td>Divalproex (valproate)</td>
<td>400–600 mg twice daily</td>
</tr>
<tr>
<td>Topiramate</td>
<td>25-200 mg daily</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>900–3600 mg daily</td>
</tr>
<tr>
<td>Botulinum Toxin</td>
<td>Dose not established</td>
</tr>
<tr>
<td>Serotonin antagonists</td>
<td></td>
</tr>
<tr>
<td>Pizotyline (pizotifen)</td>
<td>0.5–3 mg daily</td>
</tr>
<tr>
<td>Serotonin agonists</td>
<td></td>
</tr>
<tr>
<td>Methysergide</td>
<td>1–6 mg daily</td>
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**Nutritional Supplements**

<table>
<thead>
<tr>
<th>Nutritional Supplements</th>
<th>DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Riboflavin</td>
<td>400mg/day</td>
</tr>
<tr>
<td>Magnesium</td>
<td>600 mg/day</td>
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</tbody>
</table>
**Botulinum Toxin:**

Botulinum toxin (BTX) is a clostridial neurotoxin that is neurotoxic to cholinergic nerves by blocking acetylcholine release. Locally, Botulinum toxin prevents myofascial pain due to muscle spasticity by blocking muscle contraction. BTX also has analgesic effects due to inhibition of calcitonin gene-related peptide (CGRP) release from afferent nerve terminals substance P from dorsal root ganglia, and glutamate in the dorsal horn. BTX has myriad clinical benefits in treating chronic pain. It is effective in treatment of painful muscle spasticity and myofacial pain, hyperhidrosis, hypersalivation, and hyperlacrimation. BTX has been shown effective for the prevention of chronic migraine headaches chronic daily headaches. In cancer patients, BTX has been shown to improve symptoms of radiation fibrosis syndrome. It is also useful for treatment of neuropathic pain.

BTX has seven serotypes (A-G) which consist of a heavy chain bound to a light chain by a disulphide bond. The heavy chain binds the nerve terminal and facilitates internalization of the light chain. The light chain internally inhibits neurotransmitter vesicle docking on the plasma membrane. Neurotransmitter vesicular docking is mediated by the soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex which is the target for the BTX light chain. Normal nerve terminal function eventually recovers through restoration of the SNARE complex.

Clinically motor paresis and pain relief develops within five days and lasts several months. BTX is too large to penetrate the blood brain barrier and is inactivated by retrograde axonal transport; therefore there is no direct central nervous system effect.

There are three formulations of BTX currently approved for use in the United States: Onabotulinumtoxin A (Botox/Botox Cosmetic), Abobotulinumtoxin A (Dysport), and Rimabotulinumtoxin B (Myobloc).

BTX is injected into striated muscle in increments of units. Dosage units differ among the BTX products and are not comparable or convertible. BTX may be diluted in local anesthetic or sterile saline, and optimal dilutions have not been established for treatment of pain. Smaller effect or shorter duration of response seen over time due to development of antibodies against BTX. If antibodies are suspected, rotation to different serotype usually effective. Local complications include muscle atrophy, dysphagia, dysphonia, and ptosis.

Systemic complications include dyspnea, respiratory compromise, weakness, and death. Systemic complications have mostly occurred in children treated for cerebral palsy-associated spasticity and have been reported between one day and several weeks following treatment. FDA enforced a black box warning in 2009 on BTX products to highlight that BTX may spread from the area of injection to produce symptoms consistent with botulism. Symptoms such as unexpected loss of strength or muscle weakness, hoarseness or trouble talking (dysphonia), trouble saying words clearly (dysarthria), loss of bladder control, trouble breathing, trouble swallowing, double vision, blurred vision and drooping eyelids may occur.
**Tension-type Headache**
Lifetime prevalence in women 88% in women, 69% in men, 25% also suffer from migraine

**Clinical features**
- Non-pulsating, nagging, tight
- Not severe
- Usually not unilateral
- Not aggravated by physical activity
- May have photophobia, phonophobia but not both
- Lacks migraine triggering factors: changes in sleep patterns, irregular meals, menstrual cycle
- Associated with perceived life stressors and clinical depression

**Pathophysiology**
- “Muscle contraction headache” – increased EMG activity in some patients
- Myofascial-supraspinal-vascular model:
  - Association with reduced mechanical and thermal pain thresholds and low CNS 5-HT level – sensitization?

**Therapy**
**Acute treatment:**
- NSAIDs
- NSAIDs/Caffeine combinations (may lead to chronic daily headache)
- Opioid/NSAIDs combinations

**Preventive treatment**
- Tricyclic antidepressants
- Biofeedback, Relaxation
- Opioids?

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**Cluster headache**
Incidence 0.01 to 1.5%, men-to-women 2:1

**Clinical features**
- Multiple episodes of short-lived, severe, unilateral, orbital, supraorbital, or temporal pain.
- Pain is deep, constant, boring, piercing, or burning in nature
- Pain may radiate to the forehead, temples, jaws, nostrils, ears, neck, or shoulder
- Conjunctival injection
- Lacrimation
- Nasal congestion
- Rhinorrhea
- Facial sweating
- Miosis
- Ptosis or eyelid edema
- Episodic cluster 1 week to 1 year, remission at least 14 days
Usually occur at the same time each day and frequently awaken patients from sleep. Untreated duration 30 to 90 minutes. During an attack, patients often feel agitated or restless and feel the need to isolate themselves and move around.

**Treatment**

**Acute therapy:**
- Triptans
- O\textsubscript{2} through facemask for 10-15 min
- Ergotamine
- Lidocaine

**Preventive therapy**
- Verapamil
- Prednisolone taper
- Ergotamine
- Lithium
- Valproate

**Chronic Daily Headache**

**Epidemiology:** 4-5% of population

**Clinical features**
- A primary headache occurring at least 15 days per month
- A mixture of migraine and tension-type headaches, with the more severe headaches having migraine features and the less severe headaches fitting the definition of tension-type headaches.
- Most (90%) of CDH are migraine and tension headache categories.

**Etiology**
- Most (>90%) of CDH result from a transformation of a form of intermittent primary headache into a more frequent CDH pattern over a variable period ranging from months to years.
- Classification of Chronic Headache as specified by the International Classification of Headache Disorders:
  1. **Chronic migraine:** Primary HA occurring >15 days/mnth for >3 months with > 8 days/month meeting criteria for migraine.
     a. With medication overuse
     b. Without medication overuse
  2. **Chronic tension-type headache:** Primary HA occurring >15 days/month with <8 days/month meeting criteria for migraine.
     a. With medication overuse
     b. Without medication overuse
  3. **New daily persistent headache:** Chronic tension-type HA that has onset over a period of < 3 days
4. *Hemicrania continua:* (1% CHD) unique in being absolutely responsive to indomethacin. Unilateral, side-locked, and never changes in location. Moderate intensity and constant (24hrs/day, 7d/wk), steady and nonthrobbing pain

Pathophysiology not well-defined, peripheral and central mechanisms
Often attributed to excessive use of abortive analgesics (NSAIDs, Opiates, Triptans)
Psychiatric problems (unipolar depression, bipolar disease, generalized anxiety disorder, and obsessive/compulsive disorder) often accompany CDH.

**Management**

**Behavioral**
Recognition and treatment of medication overuse headache as part of initial approach to CDH
Recognition and treatment of psychiatric disorders
Relaxation techniques, biofeedback, cognitive-behavioral therapy
Changes to diet and lifestyle

**Pharmacotherapy, emphasis on prophylaxis:**
**Antidepressants**
- Amitriptyline: 25-100mg qhs
  - Not for use in patients with cardiac disease
  - Use caution in patients >60yrs
  - Use caution with conjunction with serotonin agonist agents or serotonin reuptake inhibitors
- Nortriptyline

**Anticonvulsants**
- Pregabalin
- Topiramate: 25-600mg/d
  - Not for use in patients with history of renal stones
  - Monitor for glaucoma
- Valproic acid: 250-1,500mg/d
  - Not for use in females who are pregnant or at risk for becoming pregnant
- Gabapentin: 300-2400mg/d
- Lamictal
- Depakote (weight gain, teratogenic – coadminister folate)

**Beta-blockers**
- Propranolol: 10-240mg/d
  - Monitor for depression

**Muscle relaxants**
- Tizanidine
- Flexaril

**Atypical neuroleptics (olanzapine)**

**Chronic opioid therapy (controversial)**

**Botox:** Recommended dose not established

**Opioids?**
DHE IV for 3-5 days to break the cycle of migraines while weaning off chronic analgesics causing rebound headaches

Cervicogenic Headache and Occipital Neuralgia
Cervicogenic headache prevalence (0.4 to 80%)

Clinical Characteristics
Location: Neck, occiput to whole hemicranium; Initial pain is localized posterior
Pain: unilateral, continuous, moderately severe, increased with movement
Decreased neck mobility, exacerbation of pain with neck movement
Pain responds to nerve blockade

Interventional therapy for cervicogenic headache
Nerve blocks/ Radiofrequency Neurotomy and Pulsed Radiofrequency
Neuromodulation:
- C2/C3 facet joint
- 3rd occipital nerve
- Greater occipital and lesser occipital nerves for Occipital Neuralgia
Botulinum toxin injection
Neuromodulation/ Implanted devices

Cervicogenic Headache
Pain from cervical structures is referred to the head through upper cervical roots
Occipital neuralgia is results from injury, irritation or compression to the occipital nerve

Occipital nerve

Cervical Medial Nerve Branches
Endocytosis of the intact botulinum toxin molecule is followed by disulfide cleavage and translocation into the cytoplasm.
Botulinum toxin in treatment of headache
**Miscellaneous Headaches Unassociated with Structural Lesion**
- Idiopathic stabbing headache
- Cold stimulus headache
- Benign cough headache
- Benign exertional headache
- Headache associated with sexual activity

**Organic Causes of Headache**

**Stroke**
- Hemorrhagic
- Thrombotic
- Embolic
- Headache Associated with Vascular Disorders

**Infection**
- Meningitis
- Brain Abscess
- Encephalitis
- Sinusitis
- Headache Associated with Noncephalic infections

**Inflammation**
- Temporal arteritis
- Vasculitis

**Brain Tumor**
- Primary
- Metastatic

**Structural Lesion**
- Headache Associated with Nonvascular Intracranial Disorders
- Headache or Facial Pain Associated with Disorders of Cranium, Neck, Eyes, Ears, Nose, Sinuses, Teeth, Mouth, or Other Facial or Cranial Structures
- Cranial Neuralgias, Nerve Trunk Pain, and Deafferentation Pain

**Hypertension**
- Hypertensive headache
- Malignant hypertension
- Hypertensive encephalopathy

**Other**
- Headache Associated with Substances or Their Withdrawal
- Headache Associated with Metabolic Disorders
- Headache Associated with Head Trauma
Resources:

6. FDA. Information for Healthcare Professionals: OnabotulinumtoxinA (marketed as Botox/Botox Cosmetic), AbobotulinumtoxinA (Marketed as Dysport), and RimabotulinumtoxinB (marketed as Myoblock). In: Services USDoHaH, editor; 2009.
7. FDA. Early Communication about an Ongoing Safety Review of Botox and Botox Cosmetic (Botulinum toxin Type A) and Myobloc (Botulinum toxin Type B). In: Services USDoHaH, editor; 2009.
FIBROMYALGIA

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Fibromyalgia is a common condition recognized by a constellation of signs and symptoms. These commonly consist of generalized pain, headache, fatigue, unrefreshing sleep, psychological distress, irritable bowel, paresthesia in the extremities, and morning stiffness. Severity of the symptoms varies widely. In the United States this condition affects approximately 2% of the population and is seven times more common in women than in men\(^1\).

Early in the 20th century this condition was coined ‘fibrositis’. Contrary to earlier reports, no histological changes, associated with this condition, could be identified. In 1990 American College of Rheumatology (ACR) published classification criteria\(^2\) and adapted the name of ‘fibromyalgia’ instead of ‘fibrositis’ because the latter implied existence of distinct pathological processes in the tissues\(^3\). The diagnostic criteria require the presence of widespread pain for more than three months in at least 3 quadrants of the body. In addition, to fulfill these criteria, patients must have pain on palpation at least 11 of 18 tender points in discrete locations. Diagnosis of fibromyalgia can still be made in patients with widespread pain who have fewer than 11 discrete tender points. Although associated symptoms such as sleep disturbance and fatigue are almost universally present in patients with fibromyalgia, they are not part of the diagnostic criteria. Patients diagnosed with primary fibromyalgia often report a precipitating physical traumatic event.

ACR criteria do not distinguish between primary fibromyalgia and symptoms of the disease in patients with rheumatologic, endocrine or infectious disorders such as SLE, hypothyroidism or hepatitis C (i.e. secondary fibromyalgia). Although treatment of underlying rheumatologic disorder does not typically relieve fibromyalgia, thorough rheumatologic workup of patients complaining of widespread pain is important. In particular, rheumatologist’s participation in the diagnosis is required to explore possible presence of myopathies (associated with muscle weakness), polymyalgia rheumatica and giant cell arteritis. In addition, evidence of thyroid dysfunction should be sought in patients with signs and symptoms of fibromyalgia.

Etiology of fibromyalgia remains undetermined. Many hypotheses of causes, both
peripheral and central, of this condition were advanced. Among these are endocrine and psychiatric disorders, traumatic and infectious triggers, sleep disturbance and physical deconditioning. Mounting evidence points to neuroendocrine and hormonal abnormalities, and the involvement of the central nervous system in the disease cause and progression. Notably fibromyalgia patients show disturbance in hypothalamus-pituitary axis. These manifest by lower cortisol level and blunted ACTH and cortisol responsiveness, and reduced insulin-like growth factor 1 (IGF-1) level. CSF in these patients contains elevated levels of substance P and decreased levels of serotonin and norepinephrine. Proposed peripheral mechanisms in fibromyalgia include muscle deconditioning, abnormalities in energy metabolism, as well as peripheral nerve sensitization.

Fibromyalgia is a chronic condition and available treatment is limited. In one multicenter longitudinal outcome study, except for slight improvement in overall health satisfaction, the severity of the disease remained unchanged after 7 years of follow-up. So far, no single pathogenic factor responsible for fibromyalgia has been found and both central and peripheral mechanisms appear to be involved. Although ACR criteria classify this condition based on pain and tenderness to touch, associated symptoms such as sleep disturbance and depression are essential in description of fibromyalgia. Accordingly, in absence of definitive cure of this disease, the mainstay of treatment of fibromyalgia is largely focused on addressing the entire spectrum of its signs and symptoms and possible etiologies. Specifically, management of this condition spans treating pain, the sleep disturbance, depression and muscular deconditioning. Treatment modalities include pharmacologic treatment, cognitive behavioral therapy, education about the condition, and exercise therapy.

Although drugs representing various classes were tried in treatment of symptoms of fibromyalgia, only a few these drugs were shown to be moderately effective. Conforming to the non-inflammatory nature of fibromyalgia, trials of non-steroidal anti-inflammatory medications failed to show any reduction in pain. In contrast, tramadol has been used with some success to treat fibromyalgia pain, and at least one placebo multi-center controlled study concluded that this drug is useful in treating fibromyalgia. Its mechanism of action is by serotonin and norepinephrine reuptake blockade and weak opioid agonist activity.

The use of tricyclic antidepressants in treatment of pain in fibromyalgia has been studied extensively. Mechanism of action of drugs in this class is not completely understood, but it appears to involve the reuptake of serotonin and norepinephrine in the descending spinal pathways. Several placebo controlled studies of amitriptyline alone or in combination with other agents reported an improvement in pain and sleep. In contrast, one recent study showed lack of effectiveness of amitriptyline. The choice of a tricyclic antidepressant is typically based on the side effect profile of the medication. For instance, amitriptyline should be prescribed to patients with moderate or severe sleep disturbance. Otherwise, patients may benefit from agents such as desipramine, doxepin or nortriptyline. Cyclobenzaprine, a muscle relaxant structurally similar to tricyclic antidepressants, was also shown to improve fibromyalgia symptoms in short-term trials.

Treatment of fibromyalgia with other drugs that were developed primarily for treatment of depression was investigated. In one open clinical trial venlafaxine, which, similarly to the tricyclic antidepressants, is a serotonin and norepinephrine reuptake inhibitor, appears to improve symptoms of fibromyalgia. In contrast to venlafaxine, results of the studies with selective serotonin reuptake inhibitors in treatment of pain in fibromyalgia have been mixed. Study of fluoxetine by Arnold et al shows an improvement in Fibromyalgia
Impact Questionnaire total score and the McGill Pain Questionnaire. But an earlier study by Wolfe and coworkers\textsuperscript{16} showed improvement in sleep and depression but not in pain. Combining SSRI with tricyclic antidepressants appears to improve symptoms of fibromyalgia better than either medication alone.

Encouraging results with 5-hydroxytryptamine [5-HT\textsubscript{3}] selective receptor antagonists in treatment of fibromyalgia were reported. For example, a relatively short-term double-blind, placebo-controlled study with ondansetron showed significant reduction in pain score, visual analog scale, tender point count and improvement in sleep and dizziness\textsuperscript{17}. Similar results were reported with a selective 5-HT\textsubscript{3} antagonist tropisetron\textsuperscript{18}. These outcomes are intriguing particularly in light of the evidence that 5-HT\textsubscript{3} receptor antagonists abolish anti-nociception in animals and humans\textsuperscript{19,20}. Additional studies are required to confirm the long-term efficacy of 5-HT\textsubscript{3} antagonists in fibromyalgia.

Bennett and coworkers approached the observed deficiencies in IGF-1 by treating the patients with human recombinant growth hormone\textsuperscript{21}. Improvement in general symptoms and the decrease in the number of tender points were noted in fibromyalgia patients with low level of IGF-1. Other attempts to address endocrine abnormalities associated with fibromyalgia were not as successful. For instance, although significant decrease in cortisol level was observed in some fibromyalgia patients, trials with prednisone replacement therapy did not show any benefit\textsuperscript{22}.

The role of opioids in treatment of fibromyalgia remains controversial. In spite of substantial evidence for efficacy in treating chronic pain with opioids\textsuperscript{23-26}, there is a pervasive hesitancy to use these drugs for chronic pain because of the fear of adverse side effects, such as sedation, aggravation of emotional and physical disability and the development of addiction and dependence. In response to a growing body of evidence indicating benefits of long-term opioid use by chronic pain patients, American Pain Society and American Academy of Pain Medicine have published a consensus statement\textsuperscript{27}. In this statement an important role of opioids in chronic pain treatment is recognized. This role is defined within a framework of ‘good medical practice’ whose components are proper patient evaluation, treatment plan, consultation with a specialist in pain medicine, periodic review of treatment efficacy, and documentation of the use of opioids for the treatment of chronic pain.

A prevalent concern among medical practitioners, as well as the general public, is the addiction potential resulting from opioid use. A clear distinction should be made between opioid tolerance, physical dependence and addiction. Whereas many chronic opioid users may develop tolerance and physical dependence, psychological dependence is rare\textsuperscript{28-31}. Moreover, psychological dependence and addiction need to be distinguished from pseudo-addiction. This behavioral pattern appears similar to that of an addicted patient, but is driven by unrelieved pain\textsuperscript{30,32}.

Good analgesia with tolerable adverse side effects and can be achieved by trying different agents for chronic opioid therapy. Wallace and coworkers\textsuperscript{30} showed that after a trial of four different long-acting opioid formulations effective analgesia without intolerable side effects was achieved more than 80\% of patients. Currently available opioids for chronic therapy are timed-release morphine, timed-release oxycodone, methadone, and transdermal fentanyl.

Non-restful sleep characterizes fibromyalgia in the majority of patients and contributes to the symptoms of low energy and fatigue\textsuperscript{33}. Furthermore, there are similarities in symptoms
developed by healthy volunteers with induced selective stage 4 sleep deprivation and fibromyalgia patients. In spite of strong evidence that poor sleep may result in diffuse pain and fatigue, attempts to treat fibromyalgia by correcting sleep pattern did not lead to pain relief. Notably, benzodiazepine- and non-benzodiazepine sedatives were shown to improve sleep but not to relieve other symptoms in fibromyalgia patients.

Even optimal pharmacotherapy with single or multiple agents can only have modest effect on symptoms of fibromyalgia and needs to be combined with other therapeutic modalities. One such approach is physical therapy and exercise. The rationale for this therapeutic modality is based on the evidence of muscular deconditioning in fibromyalgia patients. In fact, the lack of fitness was confirmed in more than 80% of fibromyalgia patients based on Xenon clearance and respiratory gas exchange. Several studies have demonstrated significant benefit resulting from supervised cardiovascular fitness, aerobic, strengthening and flexibility exercise programs. The short-term improvements were noted in increased physical and social function, improvement in pain and tenderness, and subjective improvement in fitness.

Initial increase in pain is often felt when patients start exercise program. This commonly leads to poor compliance and high drop out rate. To improve the outcome of patients’ participation in exercise programs a set of practical considerations was proposed by Offenbächer and Stucki. These emphasize importance of cautious initiation of the exercise program and gradual progression in frequency and intensity of the exercises. Water activities, yoga and other low-impact aerobic activities, ideally in a group setting, are recommended.

Non-pharmaceutical psychosocial management is another important approach to treatment of fibromyalgia. The main components in this approach are patient education, cognitive behavioral therapy and mind-body therapy. Some of the goals of cognitive behavioral therapy are to improve patients’ self-efficacy and provide them with coping skills. A recent study involving brief (6 sessions) cognitive behavioral therapy showed a sustained improvement in physical functioning. Improvement in pain, fatigue, sleep and other outcome measures were reported after completion of a 10-week course of mind-body therapy. Meta-analyses of multiple controlled trials and several reviews by Nielson and Weir and Morley et al. found sufficient evidence for a role of cognitive behavioral therapy in treatment of chronic pain conditions, including fibromyalgia.

Evidence and experience suggest that treatment of fibromyalgia should encompass pharmacotherapy, non-pharmacological psychosocial management, education, and exercise therapy. Even brief exposure of fibromyalgia patients to such an interdisciplinary approach resulted in significantly improved outcomes. These outcomes were measured in terms of pain severity, life interference, sense of control, affective distress, depression, perceived physical impairment, fatigue, and anxiety.

Summary

Fibromyalgia is a common disease without a known cause. Available treatment for this persistent condition is limited. Pain-all-over is the predominant symptom, but characteristically fatigue, depression and sleep disturbances are also present. Current management approaches consist of controlling the symptoms and addressing possible causes of the disease. Pharmacotherapy is moderately effective in relieving this condition. Antidepressants and other agents with activity on spinal norepinephrine and serotonin receptors appear to moderately improve pain and other symptoms. Chronic opioid treatment of
this condition remains controversial. Sustained pain control can be achieved with opioids in many chronic pain states, but the concern about the side effects and fear of abuse is an obstacle to their more widespread use.

Pharmacotherapy alone is successful in treatment of fibromyalgia only in a minority of patients, and often other treatment approaches are required. Although patients report initial increase in pain, clear benefit in physical exercise was demonstrated. The exercises should have gradual increase in intensity and consist of low-impact activities. Education and psychotherapy, in particular cognitive behavioral therapy, are another important approach to treatment of fibromyalgia. Finally, fibromyalgia patients can benefit from interdisciplinary approach consisting of pharmacotherapy, physiotherapy, education and psychosocial therapy.

REFERENCES
EVALUATION OF LOW BACK PAIN

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EVALUATION OF LOW BACK PAIN

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A. Incidence and Significance of Low Back Pain (LBP)
   - 75% of the adult population experiences pain at some time. LBP that is severe enough to require medical attention has an annual incidence of 7-15%.
   - Leading cause of disability in persons under age 50.
   - 2nd to heart disease as a cause of disability in persons over age 50.
   - Results in a loss of 93 million workdays each year.
   - Persons with LBP absorb an enormous amount of medical resources. LBP is second to upper respiratory illness as a symptomatic reason for office visits to physicians.
   - Medical expenses directly related to LBP total more than $8 billion per year and disability payments and indirect expenses are more than double that amount.

B. Anatomy of the Spine
   1. Spinal column consists of two segments
      a. Anterior segment
         1) INTERVERTEBRAL DISC (ID)
            a) Annulus fibrosus - tough peripheral fibroelastic ring
            b) Nucleus pulposus
               encapsulated by annulus fibrosus
               mucopolysaccharide with the ability to imbibe external fluid and maintain its intrinsic water balance
               - may irritate nerve roots if it spills out of the disc
         2) VERTEBRAL BODIES
         3) ANTERIOR LONGITUDINAL LIGAMENT (ALL) AND THE POSTERIOR LONGITUDINAL LIGAMENT (PLL)
            - The anterior structures are bound together by these ligaments. These ligaments provide structural support to the ID. The PLL narrows at the L5-S1 region and therefore creates an area of weakness in the ID where herniation can occur.
      b. Posterior segment
         1) INTERVERTEBRAL FORAMEN AND NEURAL STRUCTURES
         2) LIGAMENTUM FLAVUM
         3) FACET JOINTS
         4) INTERSPINOUS LIGAMENT
         5) SUPRASPINOUS LIGAMENT
2. Sacroiliac joint
   a. Classified as a true synovial joint
   b. contains synovial fluid, ligamentous connections, outer fibrous joint capsule, and cartilaginous surfaces which allow motion.

FIG. 4. The sacroiliac joint consists of a ligamentous compartment posteriorly and an articular compartment anteriorly.
C. Sources of Pain
1. Intervertebral disc - outer layer of the annulus fibrosus
2. Anterior and posterior longitudinal ligaments
3. Vertebral bodies - produce pain if invaded by metabolic or metastatic disease
4. Tissues of the nerve root in the intervertebral foramen
   a. dural sheath
   b. venules
   c. arterioles
   d. lymphatics
5. Irritated dorsal root ganglion
6. Facet joints
7. Sacroiliac joints
8. Erector spinae muscles, fascial sheaths, intramuscular septa, tendinous insertions, intramuscular blood vessels, ligaments

Fig. 1. Diagrammatic representation showing impaction between consecutive spinous processes.

Fig. 2. Diagrammatic representation showing impaction between the tip of an inferior articular process and the lamina below.

Fig. 3. Diagrammatic representation showing pain and tenderness resulting from muscle strain at the site of attachment of the iliocostalis lumborum to the angles of the ribs.

Fig. 4. Diagrammatic representation showing pain and tenderness resulting from muscle strain at the point of insertion of the lumbar intermuscular aponeurosis to the posterior superior iliac spine.
D. Evaluation of the Spine

1. History
   a. Nature of injury, previous injuries, treatments to date and efficacy, related symptoms, effect of pain on function and activities, bowel/bladder dysfunction
   b. Pain drawings

FIG. 9. Pain drawing of a typical sacroiliac joint syndrome.

FIG. 11. Pain drawing of a typical herniated nucleus pulposus.
2. Observation
   a. Spinal attitude, presence of guarding or shifts
   b. Ambulation patterns
   c. Motor weakness
   d. Asymmetrical weight bearing
3. Inspection
   a. Alignment of landmarks
   b. Lordosis, kyphosis, pelvic rotation, leg shortening
4. Tissue Tension Testing
   b. Active movements stress both contractile and noncontractile tissue
5. In Standing Position
   a. Lumbar movement - Flexion, Extension, Side flexion
   b. Toe raise
   c. Heel walk
   d. SI joint
      1) Gillet's test

FIG. 14. Gillet's test is designed to detect normal and dysfunctional sacroiliac joint motion. With normal sacroiliac joint function, when raising the right leg the posterior superior iliac spine moves inferior relative to the sacrum.

FIG. 15. With dysfunctional motion, patients will tend to compensate by tilting the pelvis. This will cause the posterior superior iliac spine to move superiorly with reference to the sacrum.
6. In Sitting Position
   a. Muscle testing - Hip flexion (L2,3), Dorsiflexion (L4), Extensor Hallucis (L4, 5), Peronei (L5, S1)
   b. Reflexes - Patellar (L3), Achilles (L5, S1, S2)
5. In Supine Position
   a. Straight leg raise
   b. Pyriformis muscle spasm
      1) active external rotation of hip
      2) passive internal rotation of hip
   c. SI Joint
      1) Patrick's test

2) Gaenslen's test
3) Hip rotation test

FIG. 20. The hip rotation test (A) is performed with the patient supine. The level of the medial malleoli is noted and a mark is placed on the skin. B: To test the left sacroiliac joint, the left leg is abducted and externally rotated. C: The left leg is then brought back to the neutral position. With normal joint mechanics, the level of the medial malleolus will appear to have moved distally with respect to the right side. D: The extremity is next abducted and internally rotated and brought back to the neutral position. E: The level of the medial malleolus with normal joint mechanics will appear to have moved proximally with respect to the right side.
8. In Prone Position
   a. Palpation of:
      1) muscle spasms
      2) trigger points
      3) facet joints
   b. SI joint
      1) Yeoman's test

E. Nonorganic signs of low back pain
   1. Waddles signs
      a. pain in back with gentle skin rolling
      b. pain with axial loading
      c. pain with axial rotation
d. significant discrepancy with pain on straight leg raising in the supine and seating position

e. nonphysiologic regional disturbances of sensation, distribution of pain or weakness

f. over-reaction, such as excessive verbalization, facial grimacing, and other pain behaviors out of proportion to the test stimulus

1. Patients with 3 or more positive Waddel signs do not respond favorably to any form of physical treatment, and surgery is not beneficial

2. Waddel’s signs are not a test for malingering and only indicate that the patient’s behavior cannot be ascribed solely to structural lesions within the spine

F. Diagnostic imaging in the evaluation of low back pain

1. Electromyography (EMG) and Nerve conduction studies (NCS)
   a. Evaluates the integrity of the anterior horn cells, nerve roots, plexus, peripheral nerves, neuromuscular junction, and muscles.
   b. Differentiates between nerve and muscle disease
   c. Helps localize the lesion and assess severity and prognosis

2. Conventional radiography
   a. Evaluates gross integrity of the spine

3. Computed Tomography
   a. Has ability to distinguish the osseous structures and most of the soft tissues of the spine

4. Magnetic Resonance Imaging
   a. Advantage over CT is greater tissue contrast therefore excels in the delineation of soft tissue, without the necessity of contrast or hospitalization (because of this, it has become the examination of choice in many spinal conditions).

5. Myelography
   a. Localizes the exact level of a lesion before surgery
   b. CT scan usually indicated first and followed with myelogram only if CT scan fails to demonstrate abnormality

6. Bone Scan
   a. Indicated if metastatic tumor, infection, trauma, arthritis, osteonecrosis or Paget’s disease suspected.

Suggested Reading


TREATMENT OF LOW BACK PAIN

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**TREATMENT OF LOW BACK PAIN**

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### A. ACUTE LOW BACK PAIN

Acute low back pain, if no neurologic symptoms are present, can be treated conservatively with bed rest and analgesics. At this stage, treatment options include brief bed rest followed by a slow resumption of physical activity. Initially sensory modulating techniques such as heat and massage can provide pain relief but as the patient returns to normal activity, these passive therapies should be replaced with active physical therapy. Also, transcutaneous electrical nerve stimulation can provide excellent pain relief in the acute phase.

**Medications**

First-line analgesics are simple ones such as aspirin or NSAIDs. If these fail then the addition of a muscle relaxant may help. If this fails, then an opioid should be tried. These medications should only be used for up to 2-3 weeks. If the patient requires these medications beyond this time, then further work-up should be performed.

**Trigger Point Injections**

If the patient complains of severe muscle spasms, then injection of local anesthetic into spastic areas of the muscle can prove beneficial.

**Epidural Steroid Injections (ESI)**

If the patient complains of radicular symptoms (see pain drawing in evaluation of low back) and fails to respond to two weeks of conservative therapy, an ESI can be very effective. A herniated disc which compresses the nerve root causes swelling and irritation. Steroids injected into the epidural space will decrease the swelling and irritation. Also, if the disc is ruptured and the disc contents spill onto the nerve, this will cause intense irritation and swelling of the nerve root. If the patient responds to one injection then a series of three injections two weeks apart is usually performed.
B. CHRONIC LOW BACK PAIN
If the patient fails to recover from the acute phase and surgically correctable causes have been ruled out through examination and radiological studies, then diagnostic and therapeutic local anesthetic injections should be performed. The choice of injection should be guided by the evaluation performed (see evaluation of low back pain).

Diagnostic and Therapeutic Injections
Facet injection
1. Intraarticular injections of a steroid local anesthetic mixture into the facet joints are both diagnostic and therapeutic. If pain relief is prolonged, repeated injections may be beneficial. If pain relief is short term but reproducible with repeat injections, then a facet denervation procedure is indicated.
2. Fluoroscopic guidance is required.
3. If unable to enter the facet (i.e. severe degenerative arthritis), then a medial branch block is indicated (figure 2).

4. Helpful when combined with physical therapy.

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**Sacral joint injection**

1. Intraarticular injections of a steroid local anesthetic mixture into the sacroiliac joint are both diagnostic and therapeutic.

2. The joint is difficult to inject, however, injections made at the superior, middle, and inferior surface are adequate to block most of the nerve supply to the joint.

3. Fluoroscopic guidance is required.

4. Helpful when combined with physical therapy.

**Trigger point injections**

1. Hyperirritable areas in the musculature of the back are called trigger points. Injection of local anesthetic into these trigger points will relax the muscle and alleviate the pain.

2. If the trigger points recur, then botulism toxin can be injected which permanently relaxes the muscle.

3. Should be combined with physical therapy.
Selective nerve root block
1. This procedure can identify the symptomatic nerve root causing the pain. Injection of a steroid mixture can give prolonged relief.
2. Fluoroscopic guidance is required.

Epidural Steroid Injection (ESI)
1. If the patient suffers from radicular symptoms, an ESI may be helpful. The longer the patient has had the symptoms, the less effective the ESI. Therefore, early treatment of radicular pain with an ESI improves prognosis. An ESI may provide temporary relief of radicular symptoms in those patients awaiting surgery.

Medications
ANTIDEPRESSANTS - Most chronic back pain patients have a disturbed sleep pattern. The tricyclic antidepressants will improve sleep as well as provide pain relief.
NSAIDS - The NSAIDS are less effective in the management of chronic low back pain. However, they may be helpful in acute exacerbations.
TRAMADOL - Tramadol is a new analgesic with weak mu opioid and weak antidepressant effects. It can be used for long term pain management.
MEMBRANE STABLIZERS - The anticonvulsants and antiarrhythmics are useful in intractable radicular symptoms which have a intermittent sharp shooting component.
OPIOIDS - If all conservative measures have failed, some chronic back pain patients can be managed on long term opioid therapy.

Physical Therapy and Rehabilitation
Whereas acute low back pain is more likely to be treated with passive physical therapy modalities, chronic back pain should be treated with active modalities such as aerobic exercises, light weight lifting, and stretching. Inactivity will increase muscle spasm therefore, patients with chronic low back pain should regularly exercise. Many low back pain patients require vocational counseling since they cannot return to their previous work level. However, modifications can be made in the patients work environment which can be both beneficial to the patient and the employer.

Psychological Counseling
Many low back pain patients suffer from depression and low self esteem. Because of the back injury, many have had their independence removed from them. Also, many pain patients suffer from anxiety which only exacerbates the pain. A psychologist is very valuable in putting things into perspective for the patient and counseling on future goals and lifestyle modification. Relaxation techniques, coping skills, and biofeedback are methods taught by the psychologist.
Neurostimulatory techniques

Transcutaneous Electrical Nerve Stimulation - This is a very cost effective treatment. If successful, the patient can wear this device which provides stimulation around the clock. It is a low risk, potentially high benefit treatment.

Dorsal column nerve stimulation (DCNS) - DCNS is useful if the patient suffers from predominately radicular symptoms. This procedure involves the placement of a quadrapolar electrode into the epidural space. Stimulation of the electrode is accomplished with an implanted generator which usually resides subcutaneously in the lower abdomen. The stimulation is felt in the distribution of the radicular symptoms and blocks pain impulses from reaching the brain. A trial stimulation period is usually performed followed by permanent implantation.

Chronic Intrathecal Drug Therapy

If the patient has failed conservative measures and complains of predominately low back pain, the delivery of opioids into the intrathecal space can provide long term pain relief. This is accomplished with a pump that is implanted subcutaneously in the lower abdomen. This pump contains a reservoir which delivers the opioid continuously through a catheter that resides in the intrathecal space. The pump is refilled percutaneously with refills required about every 1-3 months. Other drugs that can be delivered through the pump include baclofen (an antispasmodic) and local anesthetics.

Chronic low back pain and disability

Low back pain is a leading cause of disability in our society. Once it is determined that the patient suffers from chronic low back pain, a treatment plan should be carefully prepared. Once the treatment plan is completed and there is nothing further to offer the patient, the patient should be declared at maximal medical improvement (MMI). MMI means that the patient will most likely not improve with any further medical treatment. If the patient wishes to return to work, a functional capacity exam (FCE) should be performed to determine limitations. The FCE is a standardized physical examination of the patient which will give the patient's employer guidelines on modifying the work environment. If these modifications are impossible for the employer to meet, the patient may be required to seek other employment or go on disability. This disability will come from the employer (if the patient has a disability plan) or social security.

Pain as a determination of disability is very controversial. Initially, most patients go on temporary disability while medical treatment and recovery take place. Once the patient is declared as MMI, the a decision must be made if the patient will remain on permanent disability. In this situation, an impairment rating (IR) is performed which will determine the percent disability. It is rare that pain alone will result in more than 15% disability.

REFERENCES

ESTABLISHING THE DIAGNOSIS OF DISCOGENIC BACK PAIN: AN EVIDENCE-BASED ALGORhythMIC APPROACH

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KEY POINTS
1. Discogenic pain is among the most common and most challenging diagnosis the pain physician faces.
2. No single test or intervention can accurately establish the diagnosis of discogenic pain.
3. The predictive value of modalities used to diagnose discogenic pain is directly dependent on the pre-test probability of the disease.
4. With proper patient selection and standardized diagnostic criteria, discography has a high degree of predictive value for discogenic pain.

CLINICAL PEARLS
1. Effective communication is the key to success with diagnostic interventions.
2. Identify patients' usual pain distribution and character immediately prior to the procedure.
3. Educate the patient in advance about the nature and process of the diagnostic intervention they are going to have.
4. Educate the patient in advance on the proper use of the numeric rating scale (NRS) by providing specific examples of mild, moderate, and severe pain ratings.

CLINICAL PITFALLS
1. Avoid excessive sedation when performing diagnostic interventions as it may lead to increased false-negative or false-positive responses as well as increased complication rate.
2. Instruct patients to continue their usual analgesic and anxiolytic regimen prior to diagnostic interventions in order to avoid withdrawal and increased false-positive responses.

DISCOGENIC PAIN: A DIAGNOSTIC CHALLENGE
The concept of pain arising from the inter-vertebral disc (IVD) dates back to the 1940’s. Discogenic pain is among the most common and the most challenging of the diagnoses that the pain physician must confront. This premise remains as true today as it did in 1970 when Crock first described Internal Disc Disruption (IDD) characterized by radial fissures or tears through the annulus fibrosis despite a normal or near normal disc contour. The term discogenic pain refers to pain arising from the disc itself in contrast to nerve root pain caused by disc protrusion. There are many factors contributing to the complexity of this condition. These include the numerous sources of pain in the spine causing symptoms similar in distribution and character, confounding psychosocial factors, the subjective nature of pain itself and the limitations of available diagnostic tools. To further complicate the picture, there are a wide variety of diagnostic and therapeutic approaches among different specialties dealing with spine pain leading to a lack of consensus.
This chapter presents an algorithmic approach to evaluation of discogenic pain. This systematic approach provides a step-by-step process that assists the clinician to more reliably distinguish discogenic pain from other potential sources of spine pain. In order to deal effectively with the vast body of evidence and debate on the topic of discogenic pain, this chapter will begin with a review of the nomenclature and principles of diagnostic testing and medical decision-making that has been referred to so often in this literature. The role and relative contribution of each component of the evaluation process for discogenic pain will then be discussed including history, physical exam, laboratory studies, imaging and diagnostic interventions. The algorithms presented are based upon the current evidence, published guidelines, strengths and limitations of diagnostic tools and the risks and benefits of potential diagnostic and therapeutic interventions.

GENERAL PRINCIPLES OF DIAGNOSTIC TESTING

Diagnostic tests used in evaluation of spine pain may be assessed using the general principles that apply to all medical diagnostic testing. These principles are referred to frequently in the medical literature to discuss diagnostic spine interventions and are the basis of clinical decision-making. It is important for physicians dealing with spine disorders to be acquainted with this nomenclature.

The desirable features of diagnostic medical tests include accuracy, reproducibility and safety. Sensitivity and specificity are parameters used to describe accuracy. Sensitivity is a measure of false-negative rates. Specificity is a measure of false-positive rates. Figure one demonstrates the relationship among the parameters used to measure accuracy of laboratory tests. A test that is 100% sensitive, would detect all cases where the disease may be present. A test that is 100% specific would detect only those cases where the disease is certain to be present and exclude all cases where the disease is absent. In reality, diagnostic medical tests never reach this ideal level of accuracy, leaving some degree of uncertainty regarding the diagnostic information.

The gold standard is defined as a diagnostic test or benchmark that is regarded as definitive. A gold standard allows for determination of true positive results when a given diagnosis is present and true
negative results when the diagnosis is absent. The specificity and sensitivity of a given diagnostic test may then be calculated accordingly. The most commonly accepted gold standard in various medical disciplines is tissue confirmation. However, it is frequently not possible to apply a gold standard test to each individual patient. The gold standard may be impossible to perform in a living patient such as an autopsy or may carry an unacceptable level of risk such as a biopsy or surgical confirmation. In the absence of a true gold standard, the term Criterion Standard has been coined and is now the preferred term for a number of publications. The Journal of the American Medical Association defines criterion standard as a method having established or widely accepted accuracy for determining a diagnosis, providing a standard to which a new screening or diagnostic test can be compared.

Spine disorders pose yet another barrier to determination of accuracy of diagnostic tests. There is a range of anatomic features in spinal structures and a lack of correlation of these features to painful states. Tissue or surgical confirmation, even when possible, may therefore not serve as a reliable gold standard where pain is the primary outcome measure. Not surprising, diagnosis of spinal pain disorders relies far more on pain provoking or pain relieving interventions than laboratory or imaging studies.

PRINCIPLES OF MEDICAL DECISION MAKING
Despite the limitations in determining their accuracy, diagnostic tests and interventions serve a valuable purpose. When viewed from the perspective of probability, these tests and interventions help the clinician deal with the inherent uncertainty of clinical decision making. The probability that the results of a diagnostic test are valid may be influenced by factors inherent to the test such as sensitivity and specificity as well as the clinical setting in which the test is applied. Bayes’ theorem is a mathematical expression of conditional probability and a governing principle of diagnostic testing. (Figure 2) According to Bayes’ theorem, the post-test odds of a test result are directly proportional to the pre-test odds multiplied by the likelihood ratio for the test result, which is a function of the prevalence of the disease. In clinical terms, the prevalence of a disease process directly affects the meaningfulness of the test results. When the prevalence is high, there is a higher probability that a positive result indicates the presence of the disease. Conversely, interpretation of a test result in a population where the prevalence is low, has limited value.

The positive predictive value (PPV), is the proportion of patients with positive test results who are correctly diagnosed. PPV indicates the probability that a positive test reflects the underlying condition being tested for and is the most important measure of a diagnostic method. Its value does however depend on the prevalence of the disease, which may vary. Results of diagnostic tests are therefore not absolute. They must be interpreted in the context of the specific clinical conditions where the test is applied.

Fig.2-2 Bayers’ theorem

<table>
<thead>
<tr>
<th>Post-Test Odds = Pre-Test Odds X Likelihood Ratio</th>
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<tbody>
<tr>
<td>Probability Odds = ----------------- Odds</td>
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<tr>
<td>1 -Probability Probability = ----------------- 1+ Odds</td>
</tr>
<tr>
<td>Probability of Result in Diseased Person Likelihood Ratio = --------------------------------------------------</td>
</tr>
<tr>
<td>Probability of Result in Non-Diseased Person Probability of Result in Diseased Person</td>
</tr>
</tbody>
</table>

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The various measures of accuracy and reliability of diagnostic tests may be expressed in terms of validity or the soundness of diagnostic interventions. Many types of validity have been described, but the terms are not necessarily defined in a consistent manner among all practitioners. Concept validity examines the theoretical basis of a test such as anatomic or physiologic basis of an intervention. Diagnostic blocks have concept validity because a pain generator may be identified based on anatomic and physiologic basis. In effect the structure may be anesthetized therefore relieving pain. Content validity requires that a test or intervention be clearly and accurately defined. For an intervention to have content validity the clinician must adhere to the accepted definition. This allows for a valid comparison of results both within and between various samples. Face validity requires that an intervention actually achieves its intended goal on an anatomic and physiologic basis. Face validity may be established on a statistical basis using a large-scale study, by demonstrating that if content validity is achieved, then a specific result may be expected by all practitioners. Face validity may also be demonstrated on an individual basis. For example, in case of diagnostic blocks administration of contrast medium under fluoroscopic imaging may demonstrate selective spread of contrast at the target site and avoidance of spread to adjacent structures. Construct validity measures the extent to which a test correctly distinguishes the presence or absence of the condition that the test is designed to detect. Construct validity is measured using the principles of diagnostic testing and clinical decision making described above. Face validity and construct validity are critical features of any diagnostic intervention. Finally, predictive validity is a measure of the ability of a diagnostic intervention to predict successful treatment outcome. This constitutes the therapeutic utility of the diagnostic intervention.

**SOURCES OF PAIN IN THE SPINE**

Because of the multiple pain producing structures in the spine, it may be difficult to determine the exact source of back pain (Table 1). Often, discogenic pain is a diagnosis of exclusion when other areas of the spine as potential causes have been ruled out. There are many structures in the spine, which are known or have a high likelihood of producing pain. This section will discuss the different pain producing structures implicated in the production of spine pain to aid in the differential diagnosis. (Box 2-2)

**Zygapophysial Joint Pain**

Morphological studies on humans have demonstrated neuropeptides and nerve endings in the facet joint capsule. Although it remains controversial, pathology within these joints appears to result in significant back pain, which should be ruled out before diagnosing discogenic pain. Because the joints are deep structures, pain that arises from these structures radiate to other deep structures of the body via sclerotomes and myotomes, which results in a poorly localized pain pattern similar to discogenic pain. These referral patterns may result in secondary zones of reflex muscle spasm and resultant trigger points.

| □ Nerve roots  |
| □ Discs        |
| □ Facet joints |
| □ Sacroiliac joints |
| □ Vertebral bodies |
| □ Ligaments    |
| □ Soft tissues |
| □ Dura        |

**Box 2-1. SOURCES OF PAIN IN THE SPINE**
Sacroiliac Joint
As with the facet joint, there has been controversy on the sacroiliac joint (SIJ) as a cause of low back pain. However, many clinicians feel the potential for this joint to cause pain is underestimated. The SIJ is classified as a diarthrodial joint; however, with age the joint develops fibrous adhesions, which restrict movement. This restriction of movement decreases the joint's buffering capacity, which may lead to chronic pain. Like the facet joints, the SIJ is richly innervated with both free nerve endings and mechanoreceptors. The innervation has been extensively described and supports this joint as a pain sensitive structure.

Box 2-2. DIFFERENTIAL DIAGNOSIS OF SPINE PAIN

- Internal Disc Disruption (IDD)
- Disc Protrusion
- Radiculopathy
- Facet Dysfunction
- Sacroiliac Dysfunction
- Vertebral Body Fracture
- Spondylo-lysis
- Spondylo-lesethesis
- Scoliosis
- Spinal Enthesopathy
- Nerve Entrapment Syndrome
- Epidural Lipomatosis
- Diffuse Idiopathic Skeletal Hyperostosis (DISH)
- Rheumatologic Disorders
- Infection
- Malignancy
- Visceral Pathology
  - Gastro-intestinal
  - Genitourinary
  - Vascular

Intervertebral Disc
Nerve endings capable of transmitting pain impulses are abundant in the outer one-third of the annulus fibrosis in the intervertebral disc (IVD). In addition, nerves within the IVD contain neuropeptides, which are involved in pain transmission. Injuries in the annulus fibrosis may result in pain while the external appearance of the disc remains normal and before nerve roots are affected.
**Ligaments of the Spine**

There are many ligamentous structures in the spine, which are innervated with free nerve endings. However, there is variability in the density of this innervation. Of all of the ligamentous structures, the posterior longitudinal ligament appears to be the most heavily innervated with free nerve endings and the ligamentum flavum the least innervated. Degenerative changes within these ligaments may result in sensitization of free nerve endings leading to chronic pain. In addition, the close proximity of the anterior and posterior longitudinal ligaments to the discs makes these structures susceptible to exposure to the disc contents in the event of disc rupture. The disc contents may induce an inflammatory process in these ligaments leading to pain.

**Nerve Root**

The nerve root is innervated by the sinuvertebral nerve which branches from the segmental nerve and travels backward into the neural foramen. The arachnoidal covering of the nerve root is heavily innervated and a source of pain. Mechanical compression or irritation of these structures can lead to pain in the extremities that is associated with neurologic changes. The nerve root may be stimulated mechanically by disc herniation, osteophyte formation, foraminal narrowing due to degenerative disc disease, or tumor invasion. In addition, it has been postulated that both the disc contents and the facet joint contents may induce an arachnoiditis; however, Haughton et al showed this only to be true for the disc contents.

**CLINICAL EVALUATION OF THE PATIENT WITH DISCOGENIC PAIN**

**Targeted History**

History and physical examination have limited specificity for discogenic pain. However, they serve two critical functions that make the clinical evaluation the foundation for establishing the diagnosis of discogenic pain. First, and most important role of the clinical evaluation is identification of “red flags” that may indicate presence of sinister pathology. Second, it is through a careful and detailed history and physical evaluation, that the clinician will identify the population of patients with a high pre-test probability for discogenic pain. Red flags that require immediate attention include recent trauma, mild trauma or strain with a history of osteoporosis, unexplained weight loss, history of cancer, fever, pain worse at night, bowel or bladder dysfunction, intravenous drug use, pain that is not relieved in the supine position or awakens the patient from sleep.

The history should look for signs of non-discogenic pain. Although the signs taken in isolation are not very valuable, together with the physical examination and diagnostic testing, they can prove to be helpful. Lumbar facet pain is worse in the morning and with inactivity and is aggravated by extension, rotation and side bending of the spine to the diseased side. Pain from the SIJ is usually referred to the buttocks, groin, posterior thigh, and occasionally, below the knee. The pain is worsened with bending and prolonged sitting and improved with walking or standing.
Symptoms that tend to be more associated with discogenic pain include increase pain with sitting, flexion, coughing, sneezing, or activities that increase intradiscal pressure such as straining. A case report of a subject demonstrated that disc pressures progressively increased with the following positions: supine< lateral decubitus< standing< sitting< standing with forward flexion< sitting with forward flexion< standing with forward flexion against resistance< sitting with forward flexion against resistance. There are no studies that correlate these positions with the diagnosis of discogenic pain. The symptoms described in the history should not be taken as face value but rather used as a whole with physical findings and diagnostic tests.

**Physical Examination**
Like the history, the physical exam is most valuable in identifying potentially serious or harmful pathology. As such a comprehensive physical examination must be documented prior to proceeding with advanced interventional modalities.

Physical exam findings have limited specificity for diagnosis of discogenic pain. In the absence of neural compromise, the neurological exam of patients with low back pain is usually normal. The most common presentation on musculoskeletal examination is axial pain reproduction associated with decreased range of motion of the spine especially with flexion. Palpation usually reveals midline tenderness near the affected segments. There may also be evidence for increased tension in the paravertebral musculature and active trigger points.

There are a number of provocational maneuvers and examinations that may help distinguish various causes of axial spine pain and increase the pre-test probability of discogenic pain. Lumbar facet pain rarely produces true radicular pain into the extremity but because of the close association of the facet joint with the nerve root, true radicular symptoms can occur with facet joint disease (i.e., synovial cysts, facet hypertrophy, or osteophytes). Therefore, a neurological exam should be performed, especially for pain radiating below the knee, to look for nerve root compression. If side-bending results in pain on the opposite side, then soft tissue pain should be entertained. Because of the anatomical location of the facet joints, the physical examination of facet pain appears to be nonspecific and the diagnosis relies more on symptomatology and diagnostic blockade.

Because of the anatomical location of the SIJ, this structure is difficult to examine and many of the provocative tests may result in false positive responses and inter-tester variability. However, there are several provocation tests, which are easy to interpret, and reliable. Gillet's test notes the change in relationship of the upper sacral spinous process and the posterior superior iliac spine (PSIS). When the patient is standing these processes are located on the same plane. When the patient is asked to lift one leg, under normal conditions the ipsilateral PSIS will move inferiorly relative to the spinous process. In a patient with sacroiliac dysfunction, the PSIS will remain at the same level or move superiorly. Patrick's test is performed with the patient in the supine position. The patient is asked to cross one leg with the ankle placed just above the opposite knee. The examiner then pushes the knee of the crossed leg toward the floor. This test stresses the hip and the SIJ. If hip pathology is present, pain is produced in the lateral hip and groin. If SIJ pathology is present, pain is produced over the sacroiliac junction. Gaenslen's test is performed with the patient in the supine position. This test is performed by maximally flexing the hip on one side and maximally extending the hip on the opposite side. This test stresses both joints simultaneously and is positive if pain is produced over the sacroiliac junction. Yeoman's test is performed with the patient in the prone position. The hip is maximally extended by lifting the leg off the table. A positive test produces pain over the sacroiliac junction. This test may also stress the lumbar facet joints and pain produced over the lower back is positive for facet pain. The sacroiliac shear test is performed...
with the patient in the prone position. The palm of the hand is placed over the posterior part of the ilium and thrust anteriorly. This test will produce pain over the sacroiliac junction if positive. The hip rotation test evaluates the integrity of the musculature surrounding the SIJ. If SIJ pain is present, then reflex muscle spasms may limit its mobility. Under normal conditions, external rotation of the leg will lengthen the leg and internal rotation will shorten the leg. If SIJ pain is present, this lengthening and shortening will not occur.

Two additional examinations have been proposed to be more specific for detection of discogenic pain. These include centralization phenomenon (CP) and the bony vibration test (BVT). CP is the report of migration of pain towards the midline of the spine with repeated maneuvers of the spine in flexion-extension or side-bending. This pain pattern is thought to arise due to the central location of the disc, which is perceived as midline pain when stressed. This is in comparison to facet and SI joint pain, which tend to cause more lateral pain. The specificity of this test has been reported to range from 70-100% with a sensitivity of 64%. However, the time and training required for proper performance of this test limits its utility in most clinical settings and as a single physical exam maneuver, most experts agree that it is of low value and should be used together with diagnostic testing to make the diagnosis of discogenic pain. BVT involves applying a blunt electric vibrator over the spinous processes of the vertebrae. If the patient reports pain, it is suggestive of discogenic low back pain. The sensitivity and specificity of this test is controversial because studies are inconclusive due to questionable patient selection. Nonetheless, like the centralization phenomenon; it should be used together with the patient’s history and diagnostic testing to make the diagnosis of discogenic low back pain.

**Imaging And Discogenic Pain**

Imaging studies used in evaluation of painful spinal disorders may include plain radiographs, nuclear medicine scans, MRI, CT, myelography, CT myelography and single-photon emission computerized tomography (SPECT). Plain radiographs may help detect spinal instability, bony mal-alignment or deformity and the presence of degenerative disease. Nuclear medicine scans are useful in detection of tumors, fractures and infection. SPECT scans may play a limited role in identification of a subset of patients with facet disease. Prior to advances in MR imaging, myelography and CT with and without myelography were commonly employed, although not without controversy, in diagnosis and management of disc protrusion, stenotic lesions and other deformities of the spine. Currently, however, MRI is the first line imaging of choice for painful spinal disorders, thanks to its high degree of spatial resolution and the best soft tissue contrast of all the imaging modalities. All of these imaging studies have a high degree of positive predictive value where radiculopathy and nerve root compression and spinal deformities are the target diagnosis. However, where diagnosing the causes of axial spinal pain is concerned, these imaging modalities fail to provide a reasonable positive predictive value, rather they provide their greatest value in ruling out sinister pathology.

**Plain Radiographs**

Most agree that plain radiographs in two views (anteroposterior and lateral) should be the first image of choice. Plain films will demonstrate lumbar alignment, bone density and the presence of fractures and osteophytes. Addition of flexion and extension views prior to and interventional disk treatments is recommended to rule out segmental instability. Images should ideally be obtained in the upright weight-bearing posture. The disadvantage of plain radiographs is their inability to provide any information on the integrity of the discs and radiation exposure is significant. Digital fluoroscopic video assessment of the
spine in the sagittal view has been proposed as an alternative to static end-range flexion and extension images for evaluation of segmental instability. At this time there is insufficient data to support the use of this technology.

**Magnetic Resonance Imaging (MRI)**
The MRI will provide details of the spinal cord, cauda equina, discs and paraspinal soft tissue. It is the best image test to evaluate the discs. There are three changes detected on MRI that may signal discogenic pain: low signal intensity of the disc on T2 weighting, high-intensity zone (HIZ), and end plate changes.

Age-related disc degeneration results in a reduced water content resulting in a low signal intensity, or “black disc”, on T2 weighting. Although this is associated with disc degeneration, most agree that this finding is poorly correlated with discogenic pain. A study on healthy discs showed that 17% of the discs had low intensity signals and concluded that this finding has almost a 100% sensitivity but a very low specificity for discogenic low back pain. The MRI hallmark of internal disc disruption is the high-intensity zone (HIZ). The HIZ is associated with annular fissures; however, the correlation of the HIZ with discogenic low back pain is controversial. The HIZ is thought to result from inflammation resulting from the annular disruption, which leads to stimulation of pain fibers. The correlation of the HIZ to discogenic pain has a sensitivity that ranges from 81-92.5%, a specificity that ranges from 26.7-89% and a positive predictive value that ranges from 87-90%. With grade III tears, it has been suggested that the HIZ has a 100% sensitivity and specificity for discogenic pain. Although there is evidence that supports the predictive value of the HIZ for discogenic pain, HIZ is present in a large number of asymptomatic discs (incidence ranging from 25-39%) putting into question its predictive value for discogenic pain.

Degenerative disc disease often leads to changes in the vertebral endplate, which can be detected on MRI. These end plate changes are classified as Modic Type I-III changes. Type I changes, known as the inflammatory phase, are characterized by low signal intensity on T1W and high signal intensity on T2W imaging. Type II changes, known as the fat deposition phase, is characterized by high signal intensity on T1W and an equivalent or mildly high signal on T2W imaging. Type III changes, known as the bone sclerosis phase, is characterized by low signal intensity in T1W and T2W imaging. Modic changes appear to be more prevalent in patients with low back pain as compared to asymptomatic patients. Multiple studies have shown a strong correlation between modic changes, particularly type I, with chronic low back pain and positive discography. Modic changes appear to have a high sensitivity but low specificity for discogenic pain.

**Electro-diagnostics**
Electro-diagnostic testing (EDT) is an extension of the history and physical examination. Although EDT will not diagnose discogenic low back pain, it can be useful in identifying a radiculopathy as a cause of the pain. In addition, there is overlap between discogenic low back pain and radiculopathy. Most patients with radiculopathy start with discogenic pain. Because non-discogenic causes of low back pain can refer pain into the lower extremity, EDT can be useful in differentiating referred pain from radicular pain. Although EDT is useful in diagnosing lumbar radiculopathy, sensitivity is limited. EDT combined with MRI is much better in diagnosing discongenic low back pain than either modality alone.
DIAGNOSTIC INTERVENTIONS
Considering the lack of predictive value of available diagnostic imaging and EDT, it is not surprising that diagnostic interventions are so heavily relied upon for diagnosis of axial spinal pain. In the absence of correlation between objective data and subjective findings, diagnostic interventions rely on pain-provocation or pain-relief as a means of identifying the cause. These diagnostic interventions are best conceptualized as an extension of the physical examination, and not simply as imaging or laboratory tests performed in clinical medicine. The presence and level of pain ultimately remain subjective parameters and cannot be definitively confirmed or refuted unlike typical laboratory studies that may be compared to a gold standard. Therefore, there is an inherent limitation in application of the principles of diagnostic testing to these interventions. Caution is advised when interpreting measures of sensitivity, specificity or predictive values for diagnostic interventions. This however, should not be cause for alarm. When viewed from the perspective of probability, with proper application of the principles of medical decision making, and when placed in the proper context of a comprehensive medical evaluation including, history, physical exam and diagnostic imaging, the results of diagnostic interventions are valuable tools allowing the clinician and patient to select the appropriate course of therapy for painful spinal disorders. With regards to safety, diagnostic interventions have a favorable risk-benefit profile. Reports of adverse events have been limited to case reports of soft tissue infection. Although extremely rare high spinal blockade is possible with cervical and possibly thoracic MBB. Other adverse events most commonly reported include vasovagal response and headache.

Diagnostic Neural Blockade
Once sinister and non-spinal causes have been ruled out, chronic benign spine pain may be broadly divided into three categories: Neuropathic, Somatic, and Discogenic. The facet and sacroiliac joints and the intervertebral discs are common causes of somatic and discogenic pain, respectively. The combination of the comprehensive medical evaluation, imaging and neurophysiologic testing generally allow for accurate identification of neuropathic causes of spine pain. However, discrimination between somatic and discogenic pain, poses a greater challenge. It has been estimated that in the absence of disc contour abnormalities and associated neurologic findings, the comprehensive medical evaluation, diagnostic imaging, neurophysiologic testing and psychological assessment may identify the cause of low back pain in as few as 15% of patients. In contrast diagnostic neural blockade may determine the cause of spine pain and help with selection of appropriate treatment options in as many as 85% of patients.

Diagnostic neural blockade may be indicated prior to therapeutic interventions or surgery. However, diagnostic blocks are not indicated if the results will not have an impact on future treatment options or the possible therapeutic options are contraindicated for other reasons. Potential treatment options should be discussed with the patient before proceeding with diagnostic blockade.

Facet Blocks
The predictive value of lumbar MBB has been validated. With adherence to proper technique, local anesthetic blockade of the medial branch of the dorsal primary ramus does not affect adjacent spinal structures that may confound patient responses. Anesthetizing the facet joints using MBB prevents experimentally induced facet joint pain in healthy volunteers. Positive response to MBB reliably predicts successful outcome following medial branch neurotomy. The validity of cervical MBB has also
been demonstrated. A small volume of solution injected at the centroid of the cervical articular pillar remains in that location without spread to adjacent spinal structures. Cervical MBB predicts successful outcome from cervical medial branch radiofrequency neurotomy. False-negative responses to MBB caused by undetected intravascular injection of the local anesthetic are possible, but they may be eliminated by administration of contrast medium under continuous fluoroscopic examination prior to local anesthetic administration, leading to a sensitivity approaching 100%. Therefore the face validity and construct validity for these blocks has been well established. Facet joint block may also be accomplished by intra-articular local anesthetic injection. Two main limitations to this approach are failure to place the needle within the joint space and extravasation of local anesthetic outside the joint space due to defects or rupture of the joint capsule. With proper technique, intraarticular injections and MBB are of equal value in diagnostic blockade of the facet joints.

**Sacroiliac Blocks**
Diagnostic blockade of the sacroiliac joint (SIJ) is most commonly achieved by intra-articular injection of local anesthetics. However, this method may lack specificity. Local anesthetics injected in the joint space may spread to adjacent soft tissue and neural structures through defects in the ventral and dorsal capsule. Intra-articular injection of local anesthetics may also fail to anesthetize the interosseous or dorsal sacroiliac ligaments, an alternate source of SIJ pain. This may lead to false-negative responses.

An alternative to intra-articular SIJ injections is blockade of its neural innervation using local anesthetics. The SI joint is well innervated posteriorly by the medial branch of the L5 dorsal ramus and the lateral branches of the sacral dorsal rami. But controversy regarding innervation to the ventral aspect of the joint has not been fully resolved. The face validity of lateral branch blocks (LBB) of the sacral dorsal primary rami was assessed in an anatomic study by a multi-site, multi-depth injection technique demonstrating successful staining of 91% of target nerves. This is a substantial improvement compared to previously described single-site, single depth injection technique yielding a 36% success rate. A subsequent placebo controlled study in healthy volunteers demonstrated that 70% of subjects undergoing active local anesthetic blockade were protected from experimentally evoked pain from the interosseous and dorsal sacroiliac ligaments and from SIJ puncture. In comparison, only 10% of subjects in the placebo group were protected from evoked pain in the interosseous ligament and none of the subjects were protected from pain in the dorsal sacroiliac ligament or with SIJ puncture. Interestingly, LBBs did not protect the subjects from pain evoked by SIJ distension. This finding supports the possibility of ventral innervation of the SIJ and addresses prior concerns regarding distinction between intra-articular SIJ pathology versus extra-articular ligamentous structures. These findings are consistent with clinical observations. 60-89% of patients treated with radiofrequency treatment of the dorsal innervation of the SIJ experience relief of pain. However there is a smaller subset of patients who respond well to intra-articular local anesthetic and cortico-steroid injections but do not respond to radiofrequency neurotomy.

Recent data demonstrates validity of controlled blocks of the L5 medial branch and the sacral lateral branches as a predictor of radiofrequency neurotomy for the SIJ. Where as, intra-articular SIJ pathology is best assessed using intra-articular injections. The two diagnostic tests should be used systematically to assess the SIJ complex.
Provocation Discography

Lindblom in 1948 and Hirsch in 1949 are credited with the first reports of diagnostic puncture of the intervertebral disks in an attempt to diagnose the level of a disc lesion in the context of radiculopathy. The diagnostic value of discography to reproduce back and referred pain in patients with or without evidence of disc protrusion or nerve root compression, was noted subsequently by other investigators. In 1968, Holt’s seminal study of discography in asymptomatic volunteers claimed an unacceptably high false-positive rate of 37%. Since then discography has been the subject of controversy and debate.

To a great extent this controversy was related to the changing role of discography. Thanks to establishment of well-defined techniques and standardized criteria, much of the controversy has been resolved. The specificity and sensitivity of discography as an imaging study for detection of disc degeneration and disc contour abnormalities are high. Indeed, discography was originally pioneered as a morphologic test to replace or add information to myelography. This is in stark contrast to the contemporary role of discography as a physiologic, prevocational, diagnostic tool. The debate over discography is regarding its accuracy for diagnosis of discogenic pain. As with other diagnostic interventions, the primary hurdle is the absence of a gold standard. Pathological confirmation or surgical exposure may confirm presence of degenerative disc changes, but the presence or absence of discogenic pain cannot be determined by these techniques.

Twenty years after its publication, Holt’s data were subjected to re-analysis using contemporary criteria. The paper has been refuted on methodological grounds and establishment of new standards that constitute positive discography. Since then several systematic studies have been instrumental in development of criterion standards for diagnosis of discogenic pain.

The characteristic pathologic feature of IDD is the presence of radial fissures within the annulus fibrosis (AF). The Dallas discogram scale may be used to categorize these radiographic findings. There is a strong correlation between pain on discography and fissures that reach the innervated, outer third of the AF. In a controlled, prospective study in normal volunteers, Walsh demonstrated that using standardized uniform criteria, discography is 100% specific as a physiologic tool to determine if a disc is painful. Application of the new criteria to Holt’s original data resulted in a 3.7% false-positive rate per disc, a marked reduction compared to the original 37%.

In a series of studies, Carragee reported higher false-positive rates of discography in subjects with non-spine related chronic pain and subjects with abnormal psychometric profile. These studies underscore the importance of the principles of diagnostic testing in interpretation of results. (FIGURE –Bayes’ Theorem) If diagnostic testing is performed in a population with extremely low prevalence of discogenic pain, then by definition the positive predictive value of a positive response is very low. Furthermore, when the contemporary standardized criteria of Walsh are strictly applied to the data, the false-positive rates are observed at 7.1% per disc and 12.5% per patient, in contrast to 28.5% per disc and 50% per patient concluded by the study. These studies do raise an important caveat. Presence of overlap in segmental innervation and nociceptive receptor field between the intervertebral disc and adjacent structures may be a confounding factor causing an increase in false-positive rate of discography. Performance of discography on subjects with prior history of iliac crest bone graft harvest is such an example. The innervation of the iliac crest and superior gluteal region is derived from T12 – L3 dorsal rami. However, the sensory innervation of the lumbar IVD may also originate from the upper lumbar
Clinicians must be aware of other possible sources of pain in patients undergoing discography. These sources may mimic concordant pain on discography.

False-positive rates of lumbar provocation discography in asymptomatic subjects and subjects with chronic pain not related to the lumbar spine was recently subjected to systematic review and meta-analysis. Using ISIS/IASP criteria, the false-positive rate for asymptomatic subjects was demonstrated to be 2.1% per disc tested and 3% per patient. For subjects with chronic pain of non-spine origin, the false-positive rate increased slightly to 3.85% per disc and 5.6% per patient.

The impact of chronic low back pain (CLBP) on the predictive value of discography was examined by Derby. This study compared discs with grade 3 annular tears in patients with discogenic LBP to grade 3 discs in asymptomatic controls. There was no statistical difference in the pain intensity at increasing pressures between control discs in patients with LBP versus asymptomatic controls. In contrast the difference between positive discs and controls in the LBP group was substantial and easily distinguishable by patients. For example, at 50 psi above opening pressure (a.o.) the mean pain scores were as follows: asymptomatic volunteers 1.6/10, control disc in LBP group 1.1/10, positive discs in LBP group 8.7/10 (P<0.001). Therefore with standardized criteria, discography may reliably distinguish asymptomatic discs among morphologically abnormal discs in patients with chronic LBP.

The effect of abnormal psychometric profiles on discography in patients with CLBP has also been studied by Derby. In this study 81 patients with CLBP underwent psychometric testing prior to discography using the Distress and Risk Assessment Method (DRAM). Subjects were divided into four groups: normal, at risk, distressed-depressive and distressed-somatic. There was no statistically significant difference among the psychometric groups with regards to the following measures: 1. Rate of positive discograms, 2. Mean pain scores at 15, 30 and 50 psi a.o., 3. Mean pressure at initial pain response, 4. Mean volume at initial pain response. Therefore, in patients with CLBP, abnormal psychometric profiles do not appear to result in increased false-positive rates.

Somatization disorder is a particularly challenging co-morbidity in diagnosis and management of CLBP. Manchikanti studied the effect of somatization disorder and other psychiatric comorbidities on discography in a prospective clinical trial of patients with CLBP. All subjects underwent psychological testing using the Millon Clinical Multiaxial Inventory (MCMI III). The study found no difference in positive discography rates between subjects without psychiatric abnormalities compared to those with somatization disorder, depression, generalized anxiety disorder and combinations thereof. Current evidence supports use of discography as a reliable diagnostic tool in patients with somatization disorder and CLBP. Despite this, caution is advised. Patients with somatization disorder are likely to have high rates of recurrence of pain, pseudoneurologic symptoms, excessive medication use and iatrogenic illnesses. This group of patients are also hospitalized and undergo surgery three times as often as depressed patients.

Data regarding the predictive value of discography in patients with prior spinal surgery is limited. Carragee reported a false-positive discography rate of 35% per patient in the postsurgical discs of 20 asymptomatic volunteers. The implications of this study are uncertain. Although discectomy may provide symptomatic relief or remission by structural or functional alterations within the disc, there is currently no evidence that after surgical decompression, the disc becomes pain free on subsequent provocation discography. Therefore the fundamental premise of the study may not be valid. From a statistical standpoint, in this subgroup the pre-test probability of IDD is very high as the subjects have known
disease. Therefore the post-test probability of disease and the positive predictive value of the test are also high and the high discography rate may represent true presence of disease. Further research in this population is indicated.

Provocation discography is not a stand-alone measure for diagnosis of discogenic pain. When applied indiscriminately it has limited predictive value and clinical utility. However, in a population with a high pre-test probability of discogenic pain as determined by history, physical examination, diagnostic imaging and appropriate laboratory studies to rule out sinister pathology and identify other potential sources of pain, discography has been demonstrated to have a high degree of PPV for identification of discogenic pain. It is important that clinicians familiarize themselves with clinical risk factors that may lead to increased false-positive results on discography. It is equally important that clinicians utilize standardized diagnostic criteria and techniques while performing discography, in order to further reduce the false-positive responses.

AN ALGORITHMIC APPROACH TO DISCOGENIC PAIN

An algorithm may be defined as an explicit protocol with well-defined rules to be followed in solving a complex problem. Algorithms are useful ways of exploring and communicating evidence based medicine. However, although complex problems in medicine abound, the clinical solutions to those problems are rarely well defined or explicit. Patients rarely present with single well-defined pathologic findings and in the case of spine pain, coexistence of multiple pain generators is the rule and not the exception. No algorithm is therefore able to replace sound clinical judgment and each individual patient will likely require a unique treatment plan. In this section, four sets of algorithms will be explored, each addressing a component of the medical decision making process. Together these algorithms will guide the clinician from the initial presentation of axial spine pain, through comprehensive patient evaluation and ultimately establishment of the diagnosis of discogenic pain.

Chronic Pain Algorithm

Figure three summarizes the general algorithm for evaluation of the patient with persistent chronic pain. As with any chronic pain condition, chronic low back pain, especially discogenic pain, should be evaluated in the context of a multidisciplinary model. The algorithm starts with a thorough history and physical examination. The history and physical examination specific to discogenic low back pain was discussed above. The provider must first search for “red flags” requiring immediate attention or specialty evaluation. In addition, a thorough assessment of physical functioning, litigation or secondary gain and any inconsistencies in the patients reported mechanism of injury and complaints. After a thorough history and physical examination, a differential diagnosis can be established that will then guide the diagnostic pathway to be taken.

After the diagnosis of discogenic low back pain has been made, a multidisciplinary approach to management is often required since single modality physical treatments are often not enough to address the problem. This is especially true for patients that are severely de-conditioned, have litigation or coexisting psychosocial issues. If interventional therapies are recommended for the treatment of the discogenic pain, other concomitant therapies such as medication management, behavioral therapies, and physical therapies should be considered.

Frequent re-evaluation may be required during the treatment of discogenic low back pain as the patient responses are highly variable. For patients with persistent pain, the history and physical examination should be re-performed and the algorithm revisited.
Fig. 2.5 Chronic pain algorithm.
CLBP Algorithm

Figure four summarizes the initial approach to the patient with spine pain. As discussed above, the first step in evaluation of the patient with spine pain is comprehensive history and physical examination. The first question the clinician must answer is whether sinister pathology is present. Once the differential diagnosis is narrowed, the spinal causes of pain may be explored systematically. History, physical exam, imaging and EDT are highly sensitive and specific for identification of radiculopathy, with a very favorable risk-benefit profile for treatment. Therefore identification and treatment of radicular symptoms is the first step in management of spinal pain. Next attention is diverted to possible somatic causes of spine pain such as facet and SIJ disease. As previously mentioned, other potential sources of pain in the axial region should also be identified as they may mimic concordant discogenic pain. Only when radicular and somatic causes have been ruled out or treated, attention is focused on discogenic pain. This approach allows the clinician to select a population of patients with the highest pre-test probability of discogenic pain, leading to a high rate of success. This approach also ensures that more conservative lower-risk and less expensive modalities appropriate to the care of the patient are utilized first.

Fig. 2-6 Chronic low back pain (CLBP) algorithm.
Discogenic Pain Algorithm
Once patients with a high pre-test probability of discogenic pain have been identified, two questions are raised: 1. Is this patient an appropriate candidate for provocation discography? 2. Will discography results have a meaningful impact on potential treatment options? Alternatively stated, is the patient an appropriate candidate for specific treatment options that would follow diagnostic discography? If no such treatment option exists then discography should not be performed, as it has no intrinsic therapeutic value.

Figure five explores the discogenic pain algorithm. Dynamic imaging of the spine with flexion and extension radiographs in the upright weight bearing position should be performed early in the decision making process to rule out segmental instability that may preclude the patient from percutaneous disc treatments and shift the care towards surgical intervention. Low-grade degenerative spondylolesthesis without evidence of dynamic instability does not automatically preclude patients from percutaneous treatment options, but may have a negative prognostic impact and may affect the treatment options. For example electro-thermal annuloplasty may be relatively contraindicated with this picture, but treatment options with no impact on integrity of the annulus fibrosis may be well tolerated. Evidence is lacking to assist the clinician in this decision process and caution is advised.

Next advanced imaging should be evaluated, most commonly MRI. Patients with single level minimal to moderate degenerative disc disease (DDD), good disc height preservation and minimal to no evidence of a stenotic lesion are the ideal candidates for provocation discography and potential percutaneous disc treatments. Patients with three or more levels of DDD, sequestered or extruded discs, 60% or greater loss of disc height, severe degenerative changes and those with high-grade stenotic lesions, are poor candidates for percutaneous disc treatments. In these cases, discography is not routinely recommended but may be appropriate in individual cases to help determine potential treatment options. For example confirmation of single level discogenic pain in association with spondylolesthesis with absence of pain from adjacent discs may reduce a potential multilevel spinal fusion with instrumentation (based on diagnostic imaging alone) to a single level procedure with improved outcome. Alternatively, in selected cases a two-step staged treatment plan may be indicated with percutaneous disc decompression at one level followed by surgical stabilization of an adjacent level in 3-6 months’ time.

Discography Algorithm
Even in experienced hands, discography is a painful and anxiety provoking intervention. Patient preparation, establishment of a therapeutic relationship and effective communication are important keys to obtaining accurate and reliable test results as well as a satisfied patient, despite significant intra-operative and post-operative discomfort. Adherence to standardized criteria is critical in order to minimize the false-positive rate and maximize the positive predictive value of discography. The algorithm for provocation discography is summarized in figure six. Ideal predictors for discogenic pain include concordant pain ≥7/10 provoked at an indtradiscal pressure of ≤50 psi a.o. in conjunction with radiographic findings of grade-3 annular tear and the presence of a radiographically normal control disc with 0/10 pain. Failure to meet these criteria may contribute to increased false-positive rates and decreased predictive value of discography. Presence of grade-5 annular tear with extravasation of contrast medium outside the disc margin poses a special challenge. These discs may be very difficult to adequately pressurize with the usual volumes and rates of contrast administration. This may result in a higher false-negative rate and the risk of missing the diagnosis. Higher volumes and rates of contrast injection may be necessary during discography in order to adequately test these discs. Identification of grade-5 tears serves another important function of discography. Presence of full thickness tears is a risk factor for development of neurologic deficit after thermal disc lesions. Discography is mandatory prior to thermal disc treatments.
Box 2-3 provides a list of other recommendations for improved accuracy and success with discography. Discography involves interpretation of subjective information. As such, all impediments to effective communication must be eliminated in advance. Consider use of a qualified medical interpreter in case of language barrier. The patient’s usual pain distribution and characteristics must be discussed immediately prior to start of the procedure and prior to administration of sedatives or analgesics, so the concordancy of symptoms may be confirmed clearly during the test. The patient must be educated in detail about what to expect at every stage of the procedure and proper use of the numeric rating scale (NRS). Consider educating the patients about specific clinical examples of mild, moderate and severe pain and their corresponding numbers on the NRS. Other recommendations include avoidance of excessive levels of sedation during the procedure, which may result in false-negative responses. Excessive sedation may also lead to increased risk of injury during interventional therapies. Alternatively, in selected patients prone to emotional dis-inhibition, use of benzodiazepines is best avoided. For patients on chronic analgesics, patients should be instructed to continue their usual medications. This will help avoid a state of early withdrawal immediately prior to the procedure, and the potential for false-positive responses. It is recommended that needles be inserted on the asymptomatic or least symptomatic side of the patient’s spine. Once an initial pain response is provoked, consider validating the response by further confirmatory pressurization of the disc, especially when the initial pain response is sudden and short-lived. The volume of contrast administered should be kept below 3.5 ml. Increased volumes may result in false-positive responses. However, for discs with grade-0-4 annual tears or end-plate fractures, increased volume and rate of contrast administration may be necessary to achieve adequate pressurization of the disc and pain reproduction.

**Box 2-3: Recommendations for improved accuracy and success with discography**

- Communicate effectively (consider interpreter)
- Identify patient’s usual pain distribution and character in advance
- Educate patient about discography
- Educate patient in advance on proper use of the pain NRS
- Avoid excessive sedation
- Insert needles on the least symptomatic side
- Validate each pain response by confirmatory pressurization
- Keep the volume of contrast ≤3.5 ml for grade 0-4 discs
- Increased rate and volume of contrast may be necessary for grade-5 tears or end-plate fractures in order to reach 50 psi a.o.
- Continue patient’s usual analgesics prior to discography to avoid withdrawal and increased false-positive rates
CONCLUSION

The contentious publication of Holt in 1968, catapulted the topic of discogenic pain into decades of debate and controversy. However, thanks to a multitude of contributions over the last two decades from experts in both camps, we now have a far greater understanding of this condition. With an estimated prevalence of 26-39% among those with CLBP, discogenic pain is of major medical and economic concern. For many individuals with CLBP, the controversy and lack of understanding has lead to years of unnecessary suffering, misdiagnosis and maltreatment.

Due to the complexity of this condition, no single test or intervention can accurately establish the diagnosis of discogenic pain. Rather, a comprehensive and systematic investigation must be undertaken that begins with a targeted history and physical exam followed by diagnostic and therapeutic interventions and ultimately for selected individuals, culminating in discography in order to confirm the diagnosis and level of disease. An integral part of this systematic approach is strict adherence to patient selection guidelines, standardized diagnostic criteria for discography and proper technique.

Our journey towards full understanding and effective treatment of discogenic pain is not yet complete. The algorithms presented here should not only serve individual clinicians through this systematic evaluation process, but also establish a unified approach among the various specialties dealing with discogenic pain. It is through this standardized approach that we will continue to expand our understanding of this challenging condition.
REFERENCES
15. Don Tigny R: Anterior dysfunction of the sacroiliac joint as a major factor in the etiology of idiopathic low back pain syndrome. Physical Therapy 1990; 70: 250-265.


Interventional Pain Management

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THE PAIN TREATMENT CONTINUUM

The use of interventional pain management as the sole therapy for chronic pain is often met with failure. It is important to put the role of interventional therapies into context for the patient. It should be made clear to the patient that it is unlikely that interventional therapies will result in total pain relief. It is still likely that they will require other therapies for pain control. Table A summarized the pain treatment continuum.

NEURAL BLOCKADE

Neural blockade is used for diagnostic, prognostic and therapeutic purposes. Goals of the neural blockade should be clearly explained to the patient, caregiver and health care team.

Diagnostic Blockade

Diagnostically, neural blockade can be helpful in determining the anatomic source of the pain, differentiating visceral from somatic pain, and differentiating sympathetically mediated pain from somatic pain (Table B). In order to understand the diagnostic capabilities of neural blockade, it is essential to understand the anatomy of the sympathetic nervous system.

SYMPATHETIC NERVOUS SYSTEM ANATOMY

Blockade of the sympathetic nervous system is indicated in a variety of pain syndromes. As with the somatic neural blockade, knowledge of the anatomy of this nervous system is essential. The sympathetic nervous system consists of preganglionic fibers with their cell bodies located in the intermediolateral cell column of T1-L2. These preganglionic fibers leave the spinal cord via the ventral root and enter the sympathetic chain via the white ramus. The preganglionic fiber may (1) synapse with the postganglionic fiber at the level of entry, (2) travel up or down the sympathetic chain to synapse with postganglionic fibers at different levels or traverse the ganglion to reach postganglionic fibers at distant sites such as the celiac plexus, hypogastric plexus or adrenals. The post ganglionic fibers leave the ganglion to reach the target sites. There are 22 pair of sympathetic ganglion located paravertebrally from the base of the skull to the sacrum. There are 3 cervical ganglion (superior cervical, middle cervical, and inferior cervical), 12 thoracic ganglion, 4 lumbar ganglion, and 4 sacral ganglion.

None of the cervical ganglion receive white rami. Preganglionic fibers reach the ganglion by ascending in the sympathetic chain. The superior cervical ganglion lies opposite the 2nd or 3rd cervical vertebrae and represents the fused ganglion of C1-4. Branches of this ganglion include the grey rami comminantes to the upper four cervical nerves, the internal carotid plexus, the external carotid plexus, grey rami comminantes to cranial nerves VII, IX, X, and XII, and superior cardiac nerve. The internal carotid plexus provides the deep petrosal nerve to the sphenopalatine ganglion, a root to the ciliary ganglion, and fibers to the cerebral vessels and pituitary. The external carotid plexus provides branches to the submandibular ganglion and otic
ganglion. The superior cardiac nerve descends to the superficial cardiac plexus on the left side and deep cardiac plexus on the right.

The middle cervical ganglion lies at the level of the 6th cervical vertebrae and represents fused ganglion C5 and C6. Branches include grey rami to C5 and 6, a thyroid branch, and a middle cardiac nerve to the deep cardiac plexus.

The inferior cervical ganglion lies at the level of the disc space between C7 and T1. It is fused with the first thoracic ganglion in 80% of subjects to form the stellate ganglion. Branches include grey rami to C7 and C8, plexus along the vertebral artery to brain, and the inferior cardiac nerve to the deep cardiac plexus.

The thoracic ganglion all receives white rami. Branches include grey rami to the intercostal nerves, branches from T2-4 to the cardiac, posterior pulmonary and esophageal plexuses, fibers to the wall of the aorta, and branches from T5-T12 to form the splanchnic nerves to the celiac plexus (great [T5-T9], lesser [T9-T11] and least [T10-T12]).

The upper two lumbar ganglion receive white rami whereas all ganglion below the 2nd lumbar ganglion receive preganglionic fibers that descend in the sympathetic chain. Branches of the lumbar ganglion include grey rami to the lumbar nerves, branches to the aortic plexus, and lumbar splanchnic nerves to the hypogastric plexus.

The sacral ganglion branches include grey rami to the sacral nerves and nerves to the pelvic plexus.

**STELLATE GANGLION**

As discussed above, the stellate ganglion is located at the level of C7 T1. Although the technique is called a stellate ganglion block, the actual placement of the local anesthetic occurs above the stellate ganglion at the level of the middle cervical ganglion at the level of the C6 transverse process. This is to avoid the apex of the lung which is located just lateral to the stellate ganglion.

The patient is placed in the supine position and the cricoid cartilage is located. The needle entry site is just lateral to the cricoid cartilage in the groove between the trachea and carotid sheath (Figure 1). A 22g 1 1/2 inch needle is advanced posteriorly until the anterior tubercle of C6 is located. The needle is then withdrawn 1-2mm and the needle is aspirated. If blood is withdrawn, the needle is likely in the vertebral artery which enters the vertebral artery and the needle should be withdrawn and redirected (Figure 1). If the aspiration is negative, a 0.5 cc test dose should be administered. If there are no signs and symptoms of IV or subarachnoid injection, a total of 8-15cc of local anesthetic is deposited. If sympathetic blockade is desired for the head, 8cc is adequate. If sympathetic blockade is desired for the upper extremity, 15cc is required. After the injection, the patient should be placed in the upright position to allow for local anesthetic to flow down to the stellate ganglion.
Signs of an adequate sympathetic blockade to the head include ipsilateral ptosis, enophthalmos, and miosis (Horner’s syndrome). Other signs include ipsilateral lacrimation, nasal stuffiness, injected conjunctiva, and anhydrosis. The main sign of an adequate blockade to the upper extremity includes temperature increase. It is possible to get a Horner’s syndrome and still have an inadequate sympathetic blockade to the upper extremity, therefore, temperature must be monitored.

Complications of a stellate ganglion block include intrathecal or epidural injection, recurrent laryngeal block, phrenic nerve block, vertebral or carotid artery injection, cardiac accelerator nerve block (bradycardia and hypotension) and brachial plexus block. If the block is performed at C7 there is a risk of a pneumothorax.

LUMBAR SYMPATHETIC BLOCK

The lumbar sympathetic ganglion are located at the anterolateral edge of the vertebral body just anterior and medial to the psoas muscle (Figure 2). Since ganglion at L3 and below do not receive white rami, the block can be performed at the L2 ganglion which will adequately block the sympathetic supply to the lower extremity. The block is performed with the patient in the prone position. The needle entry site is approximately 5-8cm lateral to the spinous process of L2. Using a 5-8 inch 22 g needle, the needle is directed medially at approximately a 45 degree angle until contact is made on the vertebral body of L2. The needle is then withdrawn and the angle increased until the needle slides off the anterolateral edge of L2. A loss of resistance technique to air may be used since there is a nice loss of resistance as the needle passes out of the psoas muscle. The tip of the needle should be located on the anterolateral edge of the L2 vertebral body and dye should demonstrate a caudad and cephalad spread. If the dye outlines the fibers of the psoas muscle, the needle should be advanced further. 15 cc of local anesthetic should be enough to block the sympathetic supply to the lower extremity. The main indication of an adequate sympathetic blockade includes temperature increase.

Complications of a lumbar sympathetic block include local anesthetic toxicity, spinal nerve root block, subarachnoid or epidural injection, renal trauma, intervertebral disc trauma, or L1 neuralgia.

CELIAC PLEXUS BLOCK

The celiac plexus contains both sympathetic and sensory fibers to the upper GI tract and surrounding viscera. Whereas it is possible to separately block the sympathetic nervous system to the head, neck, thoracic and abdominal wall, and extremities, it is not possible to block sensation to the viscera without also blocking the sympathetic supply. Therefore, neural blockade to the viscera is discussed in this section on sympathetic neural blockade.

The upper GI tract and surrounding viscera receive sensory innervation from T5-T12 which travels through the celiac plexus. Therefore, blockade of the celiac plexus will denervate sensation to the upper GI tract (liver, stomach, pancreas, spleen, kidneys) and is commonly used for painful disease of these structures.
There are basically two techniques of celiac plexus block that will be discussed here, the transcural and retrocural approach. Each is named as the needle tip is related to the crus of the diaphragm. The block is performed in the prone position. The inferior border of the spinous process of T12 (point A) and L1 (point B) is identified. The spinous process of T12 can be located by first identifying the spinous process of T11. A line along the lower border of T11 will point to the T11 spinous process. A point C and D are marked approximately 8 cm lateral to the inferior border of the spinous process of L1 (point B). Points A, C, and D are then connected to form a flattened isosceles triangle (Figure 3). The needle entry sites are points C and D. The needles are advanced at a 45 degree angle toward point A until the vertebral body of L1 is contacted. The needle is then withdrawn and the angle increased until the needle advances off the anterolateral edge of L1. The needle tip can be placed behind the aorta (retrocrural approach) or advanced through the aorta (transcural approach or transaortic approach) (Figure 4). If the transcural or transaortic approach is used a single left sided needle is adequate with 30-50 cc of local anesthetic. If the retrocrural approach is used bilateral needle placement is required with 15-25 cc of local anesthetic on each side. The transaortic approach anesthetizes the celiac plexus directly whereas the retrocrural approach anesthetizes the splanchnic nerves.

Complications of a celiac plexus block include hypotension, local anesthetic toxicity, hematoma, hematuria, intrathecal injection, pneumothorax, neuralgia, and diarrhea. The hypotension occurs because the sympathetic supply is removed from the viscera and pooling of blood occurs. If the needle enters the kidney, transient hematuria may occur. If the needle is advanced above the 12th rib, a pneumothorax may occur. Diarrhea occurs because of the unopposed parasympathetic supply to the GI tract.

HYPOGASTRIC PLEXUS BLOCK

The hypogastric plexus is located anterior to the L5-S1 vertebrae. It supplies innervation to the pelvic viscera. Since the lumbar splanchnics innervate the hypogastric plexus directly, a celiac plexus block will not block the innervation to the lower abdominal and pelvic structures.

The hypogastric plexus is blocked with the patient in the prone position. The needle entry site is similar to the lumbar plexus block (Figure 5), but the needle is directed at a 45 degree angle mesiad and caudad until the needle tip is located just anterior to the sacral promontory. A volume of 5-8 cc of local anesthetic is administered. A lower volume is used for this block as compared to the celiac plexus block because of the close proximity of the sacral plexus.

Complications include local anesthetic toxicity, intrathecal injection, neuralgia, and sacral plexus block.

Prognostic and Therapeutic Blockade

Some patients achieve long-term pain relief that outlast the duration of the local anesthetic. When steroids are injected, pain relief can be prolonged. The therapeutic effect of a nerve block should be clearly explained to the patient. If pain relief lasts a few hours to a few days, the long-term benefit is limited. However, if the therapeutic effect of the nerve block last weeks to month, then it is reasonable to provide repeated injections over a longer period. It is generally accepted that performing repeated nerve blocks over a prolonged period should not
occur more often than 6 times per year. Examples of therapeutic blocks are epidural steroid injections, intraarticular steroid injections, trigger point injections, and sympathetic blockade. These blocks are often more efficacious when done in conjunction with physical therapy.

Prognostic blocks are often used to determine if permanent neuroablative procedures are indicated. These temporary blocks allow the patient to experience the sensory and motor deficit that the block induces.

NEURAL BLOCKADE IN THE TREATMENT OF SPINE PAIN

ZYGAPOPHYSEAL (Z) (FACETS) JOINT INJECTIONS

Goldthwaite first reported the presumptive role of Z-joints in low back pain in 1911. Since that time there have been many articles purporting to demonstrate the role of the Z-joint in spinal pain. It is only recently that a more scientific appraisal of the role of the Z-joint in spinal pain has been reported using placebo controlled blinded studies.

Anatomy

The Z-joints are synovial joints which are well innervated with nociceptors. These nociceptive fibers are carried by the medial branches of the adjacent dorsal rami.

Fibrocartilaginous meniscoids are purported to project into the joints of the lumbar and possibly cervical Z-joints. They are thought to protect the exposed cartilaginous articular surfaces during movements. The fibrous joint capsule resists bending forces and counteracts the sliding motions during extension. As well as the nociceptive fibers in the capsule, autonomic nerve fibers have been found as have synovial nociceptors. The lumbar Z-joints have a volume of 1-2 ml and the thoracic and cervical have a volume of 1 ml or less.

Maximal pressure within the Z-joint occurs with extension. In the lumbar spine, full extension may cause the inferior facet to slide past the superior facet to contact lamina which may explain pain felt by the patient on extension. The alignment of the Z-joints allows freedom of axial movement and rotation at different levels. In the lumbar spine flexion and extension is permitted, whereas axial rotation is limited. In the thoracic area rotation is permitted and flexion-extension is limited. The cervical Z-joints can be divided into the C2-3 joints and above which allow rotation and the lowest cervical joints which primarily allow flexion and extension.

History and Examination

Although careful history and examination may clinically implicate the Z-joint as a cause of the individual's spinal pain, in the lumbar spine there appears to be no specific pathognomonic clinical findings. Jackson, et al, used 127 potentially predictive variables and found none specifically correlated with pain relief on Z-joint injection. There was some correlation with older age, absence of leg pain, absence of exacerbation by cough, normal gait, absence of muscle spasm and maximum pain on extension after forward flexion. Other studies found no correlation between presenting pain in the groin, buttock, thigh, calf or foot. In this study there was no correlation between pain relief and pain provoked by passive extension and rotation movements. No patients with central back pain responded to diagnostic blocks with Z-joints. Revel, et al reported similar findings.
In the cervical region painful joints as defined by careful palpation by a trained therapist have been shown to have a good correlation with zygapophyseal joint response to injections of local anesthetics.

**Investigations**

Although X-rays, CT scans and SPECT scans can identify abnormalities and arthritis of the Z-joints, some studies have shown little correlation with relief of pain following diagnostic injections in radiologically abnormal Z-joints. The validity of reports correlating CT findings and Z-joint pain have also been questioned by Schwarzer, et al. They found marked interobserver variability in interpreting CT scans. This was despite a practice period before commencement of the evaluation and objective assessment criteria. Their conclusions were that CT had no value as a diagnostic test for lumbar zygapophyseal joint pain and single observer reporting of radiographical examination may be liable to significant error.

**Prevalence**

Using a double local anesthetic block technique where a positive diagnosis was when concordant pain relief followed the injection of a short-acting local anesthetic, and subsequently, at a different occasion, a longer acting anesthetic gave a longer duration of pain relief, Schwarzer reported isolated lumbar Z-joint pain to have a prevalence in chronic low back pain of 15%. Other authors have reported prevalence rates ranging from 7.7 to 75%.

The prevalence of isolated cervical Z-joint mediated pain in chronic neck pain may be at least 25%. If combined with provocative discography, Z-joint pain may contribute to the total pain in up to 64% in subjects with non-radicular neck pain. The incidence of thoracic Z-joint pain has not yet been reported in well-controlled studies.

Based on injection of either short-acting or long-acting local anesthetic into the joint or onto the medial branch of the dorsal primary ramus using placebo control, the incidence of false positive has been recorded as high as 38% in the lumbar and 30% in the cervical region.

**Technique**

**GENERAL PRINCIPLES:** Intra-articular zygapophyseal joint and injections of the medial branches of the dorsal primary rami which serves the zygapophyseal joints should be done under fluoroscopy. Injections not using fluoroscopy have little, if any, diagnostic value. The medial branch block has been reported to have a similar specificity as intra-articular injection for diagnostic purposes. Light sedation may be given to obviate patient movement. However, if sedation is given, full recovery needs to occur before quantification of pain relief is taken. Sedation means that concordant pain reproduction with the injection cannot be elicited. However, the reliance of concordant pain production has been doubted. All blocks should be verified with contrast to confirm correct intra-articular placement and lack of intravenous or epidural spread which would limit the diagnostic specificity of the injection.

The role of corticosteroids in any joint injectate has been questioned. These studies showed no long-term advantage of local anesthetic on its own, over local anesthetic combined with steroid or even saline. Dreyer et al, consider that the role of corticosteroids intra-articularly may be to provide a window whereby the zygapophyseal joint can be mobilized. They suggest
that an intensive period of physical therapy or chiropractics be undertaken following intra-articular joint injections. Apart from anecdotal case descriptions, no controlled studies have been reported. However, the logic has its merits, and local anesthetic and steroid placed intra-articularly may provide a period when aggressive physical therapy can have its maximum benefit in freeing up adhesions, capsular tightness and soft tissue contractures following a period of immobility due to Z-joint pain.

Despite the uncertainty of action, corticosteroid intra-articular Z-joint injections continue to be used. Open, uncontrolled studies of intra-articular cervical Z-joint injections have reported prolonged relief between 0-64% of subjects (Figure 6).

**SPECIFIC PRINCIPLES:** The patient is lain prone on the fluoroscopy table and the C-arm is maneuvered obliquely until the joint line is clearly visualized. A 22 or 25 gauge spinal needle is introduced through the skin directly in line with the direction of the fluoroscopy arm (gun barrel). The medial or lateral edge of the facet joint is touched and the needle is carefully "walked off" into the joint. Correct placement of the joint is often seen to cause a slight bend on the tip of the needle as it follows the direction of the joint. 0.1-0.2 cc of contrast is injected to confirm the intra-articular spread. As the capsule may be deficient in the superior or inferior recesses and dye may spread epidurally, it may be prudent to use a water soluble dye for the facet arthrogram.

**Thoracic Facet Injection:** With the fluoroscopy in a the AP position over the thoracic spine, a 22 or 25 gauge spinal needle is introduced at a level one lower than the C-joint to be blocked. Placing the needle parallel to the spine, approximately 1 cm from the spinal process, the needle is introduced onto the lamina just inferior to the joint to be blocked. Turning the bevel of the needle downwards, the needle is gently advanced along the lamina until it catches onto the coronally placed joint. Confirmation of intra-articular positioning can be made with a lateral view. This lateral view is often difficult to identify because of overlying ribs. Injection of 0.1 - 0.2 cc of contrast demonstrates the round discoid shape of the Z-joint on an AP appearance. Injectate containing local anesthetic with or without steroid in a volume 0.7 cc can then be introduced. Concordant pain if present should be noted during the injection.

**Cervical Z-Joint Injections:** The approach can be either lateral or from the posterior. If posterior, the C-arm needs to be positioned in a caudal cephalad direction so the joints are clearly outlined. The needle has to pass through the muscles of the neck, and thus, this approach tends to be more painful. The lateral approach has the advantage of the joints being very close to the surface and is less painful. Introduction of a 22 or 25 gauge spinal needle is done with the needle first contacting the body of the joint and slowly walking off it into the joint itself. Verification of intra-articular spread is made with 0.1 cc of contrast. The injectate volume should be less than 1 ml of local anesthetic with or without steroid. With the lateral approach care must be made regarding over-enthusiastic placement of the needle. If unsure as to the depth of the needle insertion, AP views can be taken to ensure that the needle does not go past the midline facet line on the AP view (Figure 7).

**Medial Branch Block:** The best place to block the medial branch at the lumbar spine is at the junction of the superior facet and transverse process (Figure 9). This is as it comes off the
ventral nerve over the base of the transverse process below its level of origin. A 22 gauge needle is advanced until it hits the transverse process at the medial junction of the process and the base of the superior articular process. The injection should be done slowly over 20 seconds. Each joint is innervated by at least two medial branches. It is thus necessary to block two adjacent levels. To block the L4-5 Z-joint, the L3 medial branch and the L4 medial branches need to be blocked as they go across the transverse process of L4 and L5, respectively. The L5 medial branch going to the L5-S1 Z-joint is blocked at the notch formed by the superior articular process of S1 and the ala of the sacrum. The L5-S1 joint also receives a small branch from the dorsal ramus of S1 as it emerges from the S1 posterior foramen. There is disagreement about whether this nerve needs to be blocked to anesthetize the joint. The cervical medial branch of the dorsal primary ramus position is well described and occurs in a consistent position. With a lateral approach the Z-joints of C-3/4, 4/5, 5/6 and 6/7 are anesthetized by injecting 0.5 cc of local anesthetic onto the waist of the articular pillar of the same numbered vertebrae. The nerve is held against the waist by the tendons of semispinalis capitus.

**SACROILIAC JOINT INJECTIONS**

**Anatomy**

The sacroiliac joint (SIJ) varies in size, shape and contour from side to side between individuals. The upper 25% of its superior and inferior aspect are synovial. The fibrous capsule of the joint is well formed anteriorly, but posteriorly it may have multiple tears and rents. The gluteus maximus and medius muscles have fibrous expansions which blend with the anterior and posterior sacroiliac joint ligaments. The thoracodorsal fascia attaches to the SIJ. Tightness in these structures may transmit abnormal tensions to the joint.

The main nerve supply to the joint is from the lateral branches of the posterior primary rami of L5 to S2. Additional innervations may come from L2, 3, 4, and S3. The wide innervation of this joint may explain the varied referral patterns of pain.

Movement in the SIJ is complex and probably caused by motion at other sites. It is essentially a shock absorber which, if it becomes hypomobile, may not be able to dissipate forces. This may be a factor in the production of pain. In women, SIJ motion decreases after the age of 50 and in men, after the age of 40. Pregnancy increases SIJ motion.

**History and Examination**

There appears to be no specific physical finding which accurately identifies SIJ as the source of pain. Injection of the SIJ in asymptomatic subjects caused a referral zone most constantly in an area inferior to the ipsilateral posterior superior iliac spine. Schwarzer, injecting the SIJ in patients with presumed SIJ dysfunction, reported that buttock, thigh, calf or even foot pain referral patterns were present and did not distinguish SI joint related pain from other pain generators. Groin pain was the only pain referral pattern found more commonly associated with positive response to a SIJ block. There may be an increased risk of SIJ dysfunction in patients with a lumbar fusion or hip pathology.

On examination the patient may have an antalgic gait with the trunk shifted towards the normal side. Generally, the patient tends to sit with the painful side raised and often points to the
posterior superior iliac spine as the place of greatest pain. Pain may be referred below the knee. The pain is often associated with ipsilateral paravertebral spasm and ipsilateral gluteus or piriformis spasm. Many clinical tests for sacroiliac joint dysfunction have been reported but their accuracy has not been proven by fluoroscopically guided intra-articular injections of local anesthetic.213

Prevalence
Using fluoroscopically guided articular injections in 100 patients with low back pain, Aprill reported that the SIJ was the sole source of pain in 15%. It was part of the back pain syndrome in a further 23%. Schwarzer, using a similar technique, reported that a prevalence of SI joint mediated pain to be 13-30% of the subjects tested.

Technique
GENERAL REMARKS: Many early reports of SIJ injections were non-fluoroscopically guided. The local anesthetic was usually injected, with steroid, blindly into the posterior ligamentous structures. The majority of the studies were non-controlled but still, approximately 60% of these patients were reported as showing at least some improvement. Two to four injections were usually made along the posterior SI joint line. Whether an intra-articular injection should be combined with postcapsular injections has not been investigated.

SPECIFIC TECHNIQUE: The patient is lain prone on the fluoroscopy table and the fluoroscopy or the patient angled until the inferior part of the sacroiliac joint is clearly visualized. By shifting the C-arm obliquely in some patients, the posterior aspect of the joint can be seen to be separated radiographically from the anterior aspect. The posterior aspect is seen as a more medial translucency. A 25 or 22 gauge spinal needle is introduced through the skin onto the sacrum next to the posterior inferior joint capsule. The needle is walked off until it drops into the sacroiliac joint. A lateral view should confirm the needle placement inside the joint. Occasionally, the inferior joint is extremely narrow and over-enthusiastic advancement of the needle will result in the needle being placed through the anterior capsule of the joint. 0.2-0.5 cc of contrast should confirm intra-articular placement of the needle. Concordant pain may be reproduced with the injection. On confirmation of the intra-articular spread of the contrast, local anesthetic with or without steroid can be introduced. The volume of the injectate should be no more than 3 ml. On occasions, difficulty is met with the attempt of injecting this volume. This can usually be overcome by continuing to attempt to inject while turning the needle 90 degrees. The bevel of the needle in these instances is presumably subarticular or abutting against the side wall of the joint. The sacroiliac joint injection is usually minimally painful and can be done without local sedation.

Therapy
If hypomobility of the SIJ is postulated as the cause of the patient's joint pain, injections of local anesthetics, with or without steroids, should logically be followed with manipulation and mobilization techniques together with exercises and stretching.74 Other therapies which may be of value in the acute phase of a sacroiliac joint strain, such as occurs after trauma, include an SIJ belt which must be worn tightly just above the greater trochanter, anti-inflammatories, ice in the initial stage, followed by heat and gentle stretching exercises after 48-72 hours. Physical therapy
or chiropractics should be used in the subsequent stages to mobilize the often stiff SI joint. Mobilization or manipulation techniques may involve either end of range, low amplitude, short lever arm thrust techniques, or direct oscillation techniques, together with general muscle stretching techniques. Any leg length inequality of half an inch or more may be significant in prolonging the pain syndrome and should probably be corrected. A home exercise program is important for general stretching and mobilization of the joint. Both postural and biomechanical education and correction may be necessary. An aerobic training program should also be included.

Prolotherapy is a technique which has been described to treat SIJ and low back pain. A mixture of dextrose, glycerin and phenol with a local anesthetic is injected into the ligamentous posterior capsule. It is proposed that this causes collagen formation with strengthening of proposed "weakened ligaments". The injectate itself is neurolytic and may diminish pain, not by stabilization but by denervating the posterior capsule. Control studies on these techniques are still awaited.

**DISCOGRAPHY**

Discography has been used extensively in the investigation of the painful low back. It is a topic which has aroused much debate and opposing views. The intervertebral disc has receptive nerve endings in the outer third of the annulus fibrosus and sometimes the middle third. These nerves contain neuropeptides such as substance P, vasoactive intestinal peptide, and C gene related peptide. It has long been recognized that back and leg pain can be provoked by injecting into the intervertebral disc despite lack of evidence of spillage into the epidural space and onto a nerve root. The International Association for the Study of Pain in their 1994 taxonomy have stated that, for a disc to be deemed painful, stimulation of the disc must reproduce the patient's accustomed pain (concordant pain) provided that stimulation of the disk above or below (and preferably both) does not reproduce their pain.

Internal disc disruption (IDD) describes a painful disc confined within the annulus fibrosus. The external contour of the disc may remain normal with no changes seen on CT or even on MRI. These discs have radial fissures within them which extend to the outer third of the annulus fibrosus. Here the nerve endings are exposed to inflammatory chemicals such as phospholipase A2 produced by the nuclear degeneration. This nociceptive input is translated as pain in the low back and in a somatic distribution down one or both legs. Studies looking at the concordance of pain with discography have indicated that, whereas fissures which reach only the inner third are rarely painful, 75% of the fissures which reach the outer third of the disc (grade 3) cause pain reproduction on contrast injection. Seventy-seven percent of discs with exact or similar pain reproduction exhibited grade 3 annular disruptions. MRI's may be reported as normal in the IDD as they show water content of a disc but not the morphology of a disc. In the T2 weighted image some 30% of patients with chronic low back pain exhibit a high intensity zone in the posterior annulus which is not a protrusion or a herniation. This was shown to correlate strongly with radial and circumferential fissures and reproduction of pain on discography both in the cervical and lumbar spines. Either zygapophyseal joints, the discs or both may reproduce back pain and somatic pain. This indicates both may need to be investigated by stimulation and analgesic injections. Aprill and Bogduk reported that pain reproduced by
cervical discography could be completely eliminated by subsequent Z-joint blocks at that level. The possibility of a false positive discogram suggests that negative Z-joint blockade (i.e., no pain relief) at the same level may be necessary prior to implicating the cervical disc in a pain syndrome.

**Specific Technique**

The patient is laid prone. Light sedation is given. The patient is placed in the oblique position or the C-arm is rotated obliquely. The superior articular process is positioned so it points to the junction of the posterior and middle thirds of the vertebral body above the disc to be injected. A 6 inch, 22 gauge needle is advanced immediately cephalad of the articular process and into the disc. This will cause the needle to pass inferiorly to the somatic nerve. There is a characteristic firm feel to the needle as it passes into the disc. The needle is advanced in the lateral and AP projection until the needle tip is located in the center of the disc.

The L5-S1 disc is often difficult to approach with a straight needle. A two-needle approach can be used where a curved 6 inch, 22 gauge needle is placed through an 18 gauge, 3-1/2 inch needle which is positioned onto the edge of the superior articular process of L4/L4. The curve allows the needle to miss the iliac crest. While injecting the disc, the pressure required is gauged and fluoroscopy is used to identify any leakage of the dye into the epidural space. Concordant pain may be reproduced and should be documented. A normal lumbar disc accepts 1-2 ml of water-soluble contrast. The end point of the injection is normally very firm in a normal disc and spongy with internal disc destruction or minimally degenerative discs. If the disc is herniated, there may be no end feel as the dye leaks out into the epidural space. Many injectionists will follow the injection of contrast with 0.5 ml of 1% lidocaine and possibly a small volume of corticosteroid in an attempt to decrease the pain response.

Prior to the injection the author gives the patient cephalosporin intravenously to cover for the risk of discitis. Many injectionists do not feel this is necessary. A conscientious skin cleansing is important prior to the injection to prevent introduction of skin flora.

The cervical discs can be approached from the anterior aspect up to a level of C3. After this they are approached from a more lateral oblique position. The injection should be from the right side of the patient to avoid the esophagus. The normal cervical disc holds less than 1 cc of contrast.

**EPIDURAL STEROID INJECTIONS**

The first reports of epidural injections using cocaine for low back pain and sciatica were published in 1901. In 1952 the first reports of corticosteroid injections into the subarachnoid space for the treatment of low back pain and leg pain were published. In 1972, cervical epidural steroid injections were described. Unfortunately, despite over 40 years of use and numerous studies, there is still controversy as to the usefulness, indications and frequency of epidural steroid injections. The majority of the studies have been criticized because of the small numbers of patients, the variations of inclusion criteria, lack of randomization, lack of adequate control groups, and the differences in follow-up and outcome assessment.
Rationale
Various substances are released by damage to the nucleus pulposus. One of the principal enzymes is phospholipase A2. This enzyme can initiate the inflammatory cascade by the liberation of arachidonic acid resulting in the formation of prostaglandins, leukotrienes, and peroxides. Corticosteroids act to inhibit the neuropeptide synthesis or action of phospholipase A2. They may also cause membrane stabilization of inflamed tissue and have anesthetic-like actions.

Technique
The epidural steroids may be injected by the caudal, lumbar, thoracic or cervical routes. There appears to be little common consent as to the volume of injectate or the dosages of steroids to be used. Theoretically, the injection of steroids via a trans foraminal route onto the site of the inflamed nerve root and disc should result in better clinical outcome. This still awaits clinical studies. Injecting the steroid with small amounts of local anesthetic via the transforaminal route also has the diagnostic advantage of identifying the level of the inflamed root.

If fluoroscopy is not used for the epidural injections, there is a significant failure rate. It has been reported that lumbar injections may fail to gain the epidural space in 17-30% of patients. Caudal injections have an even higher failure rate of 38%. Even if the caudal space is entered, a large volume of injectate is required to reach the lumbar epidural space.

Side effects and complications
There appears to be little risk of serious complications associated with epidural steroids. Spinal puncture in the lumbar epidural has been reported to have an incidence as high as 5%. The risk is of the steroids being injected into the subarachnoid space. Even without dural puncture there is a risk of 1% of headaches in the lumbar epidural and approximately 5% after caudal injection. The incidence of headaches following cervical epidurals is extremely high. Hyperglycemia, fluid retention, arachnoiditis, epidural abscess, aseptic meningitis and Cushing's syndrome have all been reported. In his review of 64 series of nearly 7,000 patients, Abram could not find any report of arachnoiditis as a complication of ESI. The pituitary adrenal access is suppressed for several weeks after epidural injection.

Indications
The indications are varied and often appear based on anecdotal case reports. There appears to be little or no value for patients with established radiculopathy with hard neurological signs or myelographic defects.

Results
White et al found that epidural steroid injection responses decreased within three months. Only 70% of patients in his study still had pain relief at six months. A meta-analysis of the efficacy of epidural steroid injections in the treatment of low back syndromes concluded that perhaps 14% of patients improved with ESI. It is of note that the majority of studies done did not use fluoroscopic control, and thus, the beneficial results may have been falsely low. The majority of beneficial reports were in patients with radicular sciatic pain with or without low back pain. Clinical improvement in these cases appeared to occur within a few days to a week, with improvement generally no longer than several months.
The data on cervical epidural steroids are poor. Again, the patients with radiculopathy appeared to fare better than those with other presenting features.

**MYOFASCIAL TRIGGER POINTS**

Travell and Simons described a trigger point as a hyperexcitable spot, usually within a taut band of skeletal muscle or in the muscle’s fascia. It is painful on compression and gives rise to a characteristic referred pain, tenderness and autonomic phenomena. Palpitation for trigger points may cause a twitch response in the muscle. The patient is often unaware of the trigger point although he or she may spontaneously rub the area as he or she finds it tight. On putting pressure over the point, the patient may wince or cry out and withdraw as a response to pain. This has been called the jump sign.

The pressure required to cause pain over a trigger point can be measured by a pressure threshold meter or algometer. This is a force gauge fitted with a 1 cm² rubber tip. The force required to produce pain can be measured at the trigger point. It should be a 2 kg/cm² less than the force to produce pain at a comparable site in the muscle on the opposite side of the body. The algometer can be used to objectively quantify the trigger points and to follow the results of therapy.

**Techniques of injection**

The trigger point, having been palpated with the muscle in a slightly stretched position, is affixed between two fingers. There are various methods of injecting trigger points which are well described. The needle with a syringe is inserted into the muscle until the hard band is felt and often after a twitch is seen. 0.1 to 0.2 cc of 0.25% bupivacaine is injected into this band and concordant pain in the trigger zone is looked for. The needle is then pulled out of the muscle and re-inserted along the band and a further 0.1 to 0.2 cc injected. This is done with several small injections up and down the band. Injection in small aliquots is also done across the band. The normal muscle has a softer feel than the presumed trigger point area. Importantly, after the trigger point has been injected, the patient is asked to do a range of movement exercises such as flexion and extension, and given a home exercising stretching program. Ideally, physical therapy with stretching should be done after the injection. Immediately after the injection pressure should be applied preferably with ice for a few minutes to decrease any hematoma formation from the injection.

Local anesthetic is recommended for the injectate. There is no evidence that steroids add to the efficacy and may cause systemic problems and so should probably be avoided. The type of local anesthetic, whether lidocaine, bupivacaine or procaine, has not been evaluated in comparable studies. The purpose of the injectate is:

1. To chemically break up the taut band or trigger point.
2. To desensitize the tender point and allow an increased range of movement of the muscle and the joints to which the muscle is attached.
3. To decrease the soreness following the injectate.

For low back pain the quadratus lumborum is often extremely tender to palpation. These trigger points can be injected by placing the patient with the painful side uppermost. Palpation
of the quadratus lumborum can isolate the trigger points and these can be injected via a lateral insertion.

Hopwood and Abram in 1994 reported the success rate of 59.1% in 193 patients who had trigger point injections. They stated that the main causes of failure included lack of employment, prolonged duration of pain and decreased social activity. There were no follow-up treatments given and no mention of patient education regarding perpetuating factors.

Trigger points can also be found in ligaments and capsules of joints. Injection of these areas as well as into scars can mechanically effect either the trigger points or the entrapped nerve tissue.

**NEUROLYTIC PROCEDURES**

Neurolytic procedures are generally reserved for refractory pain that has failed conservative treatment. Be cautious of neurolysis of peripheral nerves with significant cutaneous and motor innervation. In general, neurolysis is less effective for the treatment of neuropathic pain as opposed to nociceptive pain. The exception may be the newer technique of pulse radiofrequency lesioning.

Chemical neurolysis is generally reserved for cancer pain and ablation of nerve bundles (i.e. celiac plexus, hypogastric plexus. Examples are peripheral neurolysis, intrathecal alcohol/phenol, celiac/hypogastric plexus neurolysis.

Radiofrequency lesioning uses heat to ablate specific nerves. There are two techniques, high and low temperature. The high temperature technique uses temperatures as high as 90°C and ablates all nerve fibers. The low temperature technique uses temperatures of around 45°C but uses a pulsing technique. The pulse lasts 20 msec at a 300,00Hz frequency. This technique appears to be specific for ablating small unmyelinated fibers thus preserving motor and sensory. Therefore, this technique can be used on nerves that have a significant motor supply (i.e. nerve root).

Cryoablation is a technique which uses low temperatures and ablates all nerve fibers. The duration of pain relief tends to be shorter lived than chemical or radiofrequency ablation.

Intradiscal Electrothermal Annuloplasty is a new technique for the treatment of discogenic pain. Diagnostically, a discogram is performed at low pressures to determine if the disc is painful. If positive, a thermal wire coil is threaded into the nucleus pulposis of the painful disc and heated up to 90 °C. This technique will ablate the small unmyelinated fibers to the disc as well as result in a “melting” of the collagen fibers of the annulus. The annulus will then reorganize and strengthen the disc over a period of up to 6 months. The screening criteria for this procedure is found in Table C.
**MYELOSCOPY**

Myeloscopy is a new technique for spinal pain. The indications and efficacy of this procedure are in question. The current recommendations for this procedure are for lumbar radicular pain unresponsive to conservative measures (i.e. epidural steroid injection, selective nerve root injection). The method involves cannulating the epidural space via the sacral hiatus and advancing a scope up the canal via the posterior epidural space. Direct visualization of the nerve root is possible. Once visualized, either steroids can be injected or lysis of adhesions can be performed (mechanically with the scope tip or with hyaluronidase). Success is anecdotal.

**DORSAL COLUMN NERVE STIMULATION**

Dorsal column stimulation is indicated for extremity pain unresponsive to conservative measures. The technique involves placing an electrode in the epidural space and stimulating the dorsal column tracts. The level of stimulation at the spinal cord governs the distribution of stimulation. With the new synergy system, axial pain may be treated. This technique requires placement of two electrodes in the epidural space. This allows for both back and extremity stimulation. It is not recommended that stimulation be tried for pure axial pain. Of patients that have 50% or greater pain relief at the time of implant, there is about a 36% long-term success (continued pain relief of greater than 50%)

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**REFERENCES:**


Interventional Therapies for Chronic Pain: Indications and Efficacy

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Running Title: Interventional Therapies for Chronic Pain

Educational Objectives: 1) To discuss the scientific evidence regarding the efficacy of new and emerging minimally-invasive treatments for spine-related pain, including radiofrequency treatment intradiscal therapies. 2) To discuss the scientific evidence regarding the safety and efficacy of intrathecal drug delivery for the treatment of cancer-related and noncancer pain.

Minimally-Invasive Treatments for Spine-Related Pain

Introduction
Interventional pain therapy refers to a group of targeted treatments used for specific spine disorders, ranging from epidural injection of steroids to percutaneous intradiscal techniques. Some have been rigorously tested in randomized controlled trials (RCTs), whereas others are in widespread use without critical evaluation. When these treatment techniques are used for the disorders they are most likely to benefit (Table 1), they can be highly effective; however, when used haphazardly, they are unlikely to be helpful and, indeed, may cause harm.

Definitions
Low back pain, a nonspecific term, refers to pain centered over the lumbosacral junction. To be precise in our approach to diagnosis and treatment, we differentiate pain primarily over the axis of the spinal column from that which refers primarily to the leg (Figure 1). Lumbar spinal pain is pain inferior to the tip of the twelfth thoracic spinous process and superior to the tip of the first sacral spinous process. Sacral spinal pain is inferior to the first sacral spinous process and superior to the sacroccygeal joint (1). Lumbosacral spinal pain is pain in either or both regions and constitutes “low back pain.” Other patients present with “sciatica,” or pain predominantly localized in the leg. The proper term, however, is radicular pain because stimulation of the nerve roots or the dorsal root ganglion of a spinal nerve evokes the pain.

Pathophysiology
The basic functional unit of the spine is the functional spinal unit and comprises two adjacent vertebral bodies with two posterior facet joints, an intervertebral disc, and the surrounding ligamentous structures (Figure 2). The intervertebral disc absorbs energy and distributes weight evenly from one spinal segment to the next while allowing movement of the protective bony
elements (2). Lifting, bending, twisting, or whole-body vibration can damage elements of the spine. With injury and aging, progressive degenerative changes appear in each element of the functional spinal unit, along with the onset of characteristic symptoms (Figure 2). The earliest change in the lumbar facet joints is synovitis, which progresses to degradation of the articular surfaces, capsular laxity and subluxation, and finally enlargement of the articular processes (facet hypertrophy). Progressive degeneration also occurs within the intervertebral discs, starting with loss of hydration of the nucleus pulposus followed by the appearance of circumferential or radial tears within the annulus fibrosis (internal disc disruption).

Lumbosacral pain can arise from the facet joints or the annulus fibrosis (3). With internal disruption of the annulus, some of the gelatinous central nucleus pulposus can extend beyond the disc margin, as a disc herniation (herniated nucleus pulposus; HNP). When HNP extends to the region adjacent to the spinal nerve, it incites an intense inflammatory reaction (4). Patients with HNP typically present with acute radicular pain. Hypertrophy of the facet joints and calcification of the ligamentous structures can reduce the size of the intervertebral foramina and/or central spinal canal (spinal stenosis), with onset of radicular pain and/or neurogenic claudication.

Patients with prior lumbar surgery and either recurrent or persistent low back pain, often termed failed back surgery syndrome, need mention (5). Knowing the type of surgery, the indications for and results of the surgery, and the time course and characteristics of any changes in the pattern and severity of postoperative pain, is essential. Recurrent pain or progressive symptoms signal the need for further diagnostic evaluation.

**Initial Evaluation and Treatment**

In first evaluating a patient with low back pain, several features in the history - “red-flag” conditions - require prompt investigation, including new onset or worsening back pain after trauma, infection, or previous cancer. Patients with progressive neurologic deficits (typically worsening numbness or weakness) or bowel or bladder dysfunction, also warrant immediate radiologic imaging to rule out a compressive lesion (6).

If no red-flag condition is apparent, diagnosis and treatment rely on location and duration of symptoms, and determining if the pain is acute or chronic and primarily radicular or lumbosacral in nature. Acute low back pain is pain that is present for less than three months, while chronic low back pain is defined as being present for a longer period of time. (1)

**Acute radicular pain**

HNP typically causes acute radicular pain, with or without radiculopathy (signs of dysfunction including numbness, weakness, or loss of deep tendon reflexes referable to a specific spinal nerve). In elderly patients and those with extensive lumbar spondylosis, acute radicular symptoms caused by narrowing of one or more intervertebral foramina can occur (7). Initial treatment is symptomatic, and following HNP, symptoms resolve without specific treatment in about 90% of patients (8). For those with persistent pain after HNP, lumbar discectomy may be indicated. A controlled trial of surgical versus non-operative treatment showed significant improvement in both groups over two years, but was inconclusive about the superiority of either approach (9).
**Chronic radicular pain**
Persistent leg pain in the distribution of a spinal nerve may occur in patients with a disc herniation with or without subsequent surgery. In those with persistent pain, a search for a reversible cause of nerve root compression is warranted. In many individuals, scarring around the nerve root at the operative site can be seen with magnetic resonance imaging (MRI) (10), and electrodiagnostic studies show a pattern suggesting chronic radiculopathy (11). This patient group has characteristics similar to those suffering from other nerve injuries, and initial management should consist of pharmacologic treatment for neuropathic pain (12).

**Acute lumbosacral pain**
Most patients presenting with acute onset of lumbosacral pain without radicular symptoms have no obvious abnormal physical findings (13), and radiologic imaging is unlikely to be helpful (14). Traumatic sprain of the muscles and ligaments of the lumbar spine or the zygoapophyseal joints, and early internal disc disruption, are significant causes of acute lumbosacral pain. Similar to patients with acute radicular pain, this group is best managed symptomatically.

**Chronic lumbosacral pain**
There are many causes of chronic lumbosacral pain, and identification of the anatomic cause cannot be done with certainty in up to 90% of cases (6). The structures most commonly implicated include the sacroiliac joint, lumbar facets, and lumbar intervertebral discs. In chronic low back pain, the incidence of internal disc disruption has been estimated to be 39% (range 29-49%), facet joint pain, 15% (10-20%), and sacroiliac joint pain, 15% (7-23%) (15). The gold standard for diagnosing sacroiliac and facet joint pain is injection of local anesthetic at the site (16). However, the use of uncontrolled local anesthetic blocks for diagnostic purposes is plagued by high placebo response (17). For patients achieving significant short-term pain relief with diagnostic blocks, radiofrequency treatment offers a simple, minimally invasive intervention that can provide pain reduction for three to six months in those with facet-related pain. Pain from degenerating intervertebral discs is also a source of chronic axial back pain (15). Diagnostic provocative discography may identify symptomatic discs prior to management with therapies such as intradiscal electrothermal therapy (IDET) or surgical fusion.

**Medical Therapies**
Numerous pharmacologic agents and minimally invasive treatments are beneficial in treating specific types of pain. There is no consensus on how these therapies should be sequenced in treating persistent low back pain; the general approach to utilizing each therapy is shown in Table 1.

**Neuropathic pain medications.** Treatments of neuropathic pain such as chronic lumbar radicular pain are extrapolated from RCTS examining common forms of neuropathic pain: painful diabetic neuropathy, and post-herpetic neuralgia (18, 19). Tricyclic antidepressants (TCAs; e.g., nortriptyline, desipramine) and newer selective norepinephrine reuptake inhibitors (SNRIs; e.g., venlafaxine, duloxetine) are effective in the treatment of neuropathic pain (18, 19). Antiepileptic drugs (e.g., gabapentin, pregabalin) also can effectively treat neuropathic pain (18, 19). Decisions regarding pharmacologic treatment of neuropathic pain may be based on an analysis of the number needed-to-treat (NNT); the NNT (with 95% confidence intervals) are: TCA, 3.1 (2.7-3.7); SNRI, 6.8 (3.4-4.41); and gabapentin/pregabalin, 4.7 (4.0-5.6) (19).
**Interventional therapies**

**Epidural injection of steroids.** Numerous RCTs have examined the efficacy of epidural corticosteroid injection for acute radicular pain. Such injections into the epidural space are thought to combat the inflammatory response that is associated with acute disc herniation (20). In acute radicular pain with HNP, the evidence (20-22) shows that epidural steroids reduce the severity and duration of leg pain if given between 3 and 6 weeks after onset. Adverse effects, such as injection site pain and transient worsening of radicular pain, occur in less than 1% of treated subjects (22). Beyond 3 months from treatment, there appear to be no long-term reductions in pain or improvements in function (22). This therapy has never proven helpful for lumbosacral pain without radicular symptoms.

**Facet blocks and radiofrequency treatment.** Pain from the lumbar facet joints affects up to 15% of chronic low back pain patients (23). Patients are identified based on typical patterns of referred pain, with maximal pain located directly over the facet joints and patient report of pain on palpation over the facets; radiographic findings are variable, but some degree of facet arthropathy is typically present (24). A few low-quality studies suggest that the intra-articular injection of anesthetics and corticosteroids leads to intermediate-term (1 – 3 months) pain relief in patients with an active inflammatory process (23). Radiofrequency denervation delivers energy through an insulated, small-diameter needle positioned adjacent to the sensory nerve to the facet joint, creating a small area of tissue coagulation that denervates the facet joint. Two systematic reviews concluded that there is moderate evidence that radiofrequency denervation provides better pain relief than sham intervention (25, 26). The quality of the six available RCTs was deemed adequate, but they were conducted in technically heterogeneous manner (e.g., varying inclusion criteria, differing treatment protocols), thus limiting analysis of their findings. Approximately 50% of patients treated report at least 50% pain reduction. Pain typically returns six and 12 months after treatment, and denervation can be repeated without lessening of efficacy (27). Adverse events are uncommon; in 1% of treated patients, pain at the treatment site lasted two weeks or less (28).

**Intradiscal electrothermal therapy.** The intervertebral disc is thought to be involved in 29% to 49% of patients with chronic low back pain (29). Provocative discography is a controversial diagnostic test that employs a series of needles placed in the central portion of the intervertebral discs; a small volume of saline or radiographic contrast is then introduced to try to reproduce the patient’s typical pain, to determine the offending disc. This test has been used to select patients for surgical fusion, but its ability to predict outcome is questionable (29).

Discography has also been used to select patients for a procedure called IDET, which is used to treat discogenic chronic lumbosacral pain. IDET employs a steerable thermal resistance wire placed along the posterior annulus fibrosus. Thermal energy is applied to destroy penetrating nociceptive fibers and to change the cross-linking of glucosaminoglycans, thereby stiffening the intervertebral disc (30). Clinical study results are mixed; one high-quality RCT showed that 40% of patients achieved greater than 50% pain relief, while 50% of the patients had no appreciable benefit (NNT to achieve 75% relief of pain = 5) (31). A second high-quality RCT showed no effect (32). When all studies are combined, a 50% reduction in pain is suggested, as is improvement in sitting and standing tolerance in 40-50% of patients receiving IDET at a single level, with concordant discography and well-preserved disc height (33). Despite ongoing reports of successful use of IDET (34), recent evidence-based guidelines for nonsurgical low back pain interventions found little evidence for use of IDET (35).
Percutaneous discectomy: Plasma disc decompression and other emerging techniques.

The development of minimally invasive, percutaneous techniques to treat lumbar disc herniations and persistent radicular pain has had a long history, starting with chemonucleolysis using chymopapain and evolving through a series of techniques, from laser-assisted disc decompression through radiofrequency-based techniques like plasma disc decompression (nucleoplasty). Many of these techniques have undergone extensive clinical testing and failed to show efficacy comparable to open discectomy using an operative microscope. Nonetheless, ongoing interest in further developing effective percutaneous interventions to treat small symptomatic disc herniations continues. Our group has recently published long-term outcomes of an RCT comparing nucleoplasty to transforaminal injection of steroid in a cohort of patients with persistent radicular pain associated with contained disc herniations, demonstrating durable reduction in pain and improvements in functional status two years after treatment (36).

Intrathecal Drug Delivery for Chronic Pain

Introduction and patient selection

Before considering implantable therapy, the patient should have progressed through the pain treatment continuum or the World Health Organization ladder. This assures that the patient has been given a fair trial of more conservative therapies before embarking on invasive pain treatment. One area of controversy is understanding when a spinal cord stimulator should be utilized versus a spinal drug delivery system. Spinal cord stimulation is considered a more conservative therapy, since there are no drugs involved and there is less utilization of the healthcare system for management (37). As discussed below, with newer spinal agents for neuropathic pain, the decision to use spinal cord stimulation or spinal drug delivery should be based more on pain distribution. With advancements in the technology of spinal cord stimulation, this view may become obscure. The current recommendation is spinal cord stimulation for axial pain with extremity pain and spinal drug delivery for axial or trunkal pain, or pain unresponsive to spinal cord stimulation.

Nociceptive pain is mediated by an intact and functioning nervous system. Neuropathic pain is elicited by a damaged peripheral or central nervous system. Historically, it was thought that nociceptive pain is more responsive to intrathecal drug therapy whereas neuropathic pain is more responsive to spinal cord stimulation. However, with the development of non-opioid drugs, this consensus may no longer hold. Preclinical studies have demonstrated that the spinal delivery of agents such as clonidine, sodium and calcium channel blockers are more effective than opioids in treating neuropathic pain (38). With these better drugs and better technology for spinal cord stimulation, definite lines between spinal cord stimulation and spinal drug delivery are obscured (37).

Another area of controversy is the absence or presence of a known pain generator. Should patients without an identified pain generator be managed with implantable devices? An example is the low back pain patient with normal imaging studies, no physical findings, and negative diagnostic injections. These patients present a dilemma, since undiagnosed psychological disorders may be overshadowing the problem. Objective evidence of pathology is more important for non-malignant pain than for malignant pain because of psychological issues that surround pain of unknown etiology. It is not to say that patients without objective evidence of pathology should be excluded, rather they should be evaluated closely for psychological issues.
(discussed below). If they are declared psychologically stable for implantation, then one should proceed even in the absence of objective pathology (39).

Historically, it has been a requirement to demonstrate some response to systemically administered opioids. The decision to proceed with spinal drug delivery was usually made if the patients experienced a partial, unacceptable response or unacceptable side effects in spite of adequate pain relief. The absence of any appreciable pain relief at reasonable doses of an opioid in a nociceptive pain patient probably precludes the use of intraspinal opioids. However, this criteria is controversial for neuropathic pain. It has been demonstrated in the Chung model of neuropathic pain that intrathecal opioids are ineffective in relieving pain whereas systemic opioids are effective (40). This is an example of where a partial response of a systemically administered opioid in no way predicts the effect of the intrathecal opioid. This explains why some patients still require systemic opioids in addition to the spinal non-opioid agents. However, most patients that demonstrate some response to systemic opioids will respond to spinal opioids. A general rule of thumb is that the closer the injury is to the central nervous system, pharmacological therapy will become less and less effective whether you are using opioids or non-opioids. Demonstration of opioid responsiveness is a strict criteria and, if used, there will be less failures. In severe cases, neuropathic pain often cannot be effectively managed with a non-opioid alone. The non-opioid is usually added to the opioid to enhance analgesia.

Psychological screening

Most experts will agree that psychological screening is mandatory prior to embarking on chronic intraspinal drug therapy. In spite of this consensus, there are few reports on the efficacy of psychological screening in predicting outcome. This probably reflects the research challenges in this area, and the difficulties in predicting long-term success based on psychological screening. However, there are some reports in the literature supporting psychological screening, and in general these studies find that patients with a psychological profile deemed appropriate for implantable therapy have better outcomes than those deemed inappropriate (41). However, there are some early reports that question the utility of a psychological evaluation in predicting outcome. Several studies state that depression, hysteria, and hypochondriasis are common in pain patients and do not constitute a contraindication to implants (42-45). Burton went as far as to question the need for psychological evaluation per se, but did admit that psychological testing can identify significant problems that may interfere with long-term success (42). There have been others that have agreed with this belief (46); however, specialists with the most experience with implantables for pain relief hold strong to the belief that psychological screening is crucial to the long-term success of implantables for chronic pain management (47). Most of this literature involves spinal cord stimulation, however, this information can be applied to chronic intraspinal drug delivery. Most of the studies in this area use the Minnesota Multiphasic Personality Inventory (MMPI) as a predictor of outcome with spinal implantables. North et al. (48) reported on the predictive value of psychological testing on the outcome of spinal cord stimulation. He concluded that low scores on two psychological traits, anxiety and problems with authority (as measured by the Derogatis Affects Balance Scale and the Wiggins scales of the MMPI, respectively) predicted pain relief following a spinal cord stimulation trial but not three months after permanent electrode implantation. These authors pointed out that their sample could have been biased, but they still supported psychological screening. Burchiel et al. (49) studied 40 patients with chronic low back and leg pain who underwent spinal cord stimulation. They used the MMPI, the visual analogue pain rating scale (VAS), the McGill Pain
Questionnaire (MPQ), the Oswestry Disability Questionnaire, the Beck Depression Inventory, and the Sickness Impact Profile to predict treatment outcome. Regression analysis revealed that increased patient age and MMPI D subscale scores correlated with poor outcomes. Higher scores on the evaluative subscale of the MPQ correlated with an improved outcome. From this study, they developed the following equation which correctly predicted success or failure at three months in 88% of their patients: % delta VAS = 112.57 – 1.98 (D) – 1.68 (Age) + 35.54 (MPQe). Brandwin and Kewman (50) found that treatment-resistant patients had relatively lower hysteria and hypochondriasis scores than the successful patients. They also concluded that higher elevations of the depression scale were associated with treatment failure. Daniel et al. (51) used a six-point rating scale based on the results of a psychological interview, a pain questionnaire, a health index, the Cornell Medical Index, the McGill Pain Questionnaire, the Beck Depression Inventory, and the MMPI. They reported a 76.5% accuracy in the psychologists predicting outcome based on this scale. In a focus article, Nelson et al. (52) summarized certain psychological-behavioral features that would exclude a patient from further consideration for implantable therapy. These include the following:

a. **Active psychosis.** A psychotic patient can have very real pain but their perception of the pain is often distorted. If the psychotic patient is stabilized on neuroleptics, they may be reconsidered for implantation but carefully monitored.
b. **Active suicidality.** Stabilization of the suicidal thoughts and associated mood disturbances is necessary before further consideration.
c. **Active homicidality.** It is quite difficult to stabilize these individuals and they are often too unstable to engage in any treatment of this sort.
d. **Major uncontrolled depression or other mood disorders.** Patients with severe depression may experience increases in pain. If the depression is treated, there pain may decrease significantly to eliminate the need for invasive therapy.
e. **Somatization disorder or other somatoform disorders.** These patients are at risk of developing other symptoms in response to the implant. This exclusionary criteria should be used with caution as many chronic pain patients have vague pain complaints with no identifiable etiology.
f. **Alcohol or drug dependency.** Patients with major alcohol or drug problems who demonstrate a minimum of three months of appropriate control of substance use may be reconsidered.
g. **Compensation or litigation resolution.** Although treatment obstacles may occur if the patient has a monetary incentive to remain disabled by pain, most pain experts agree that these patients should be evaluated on a case-by-case basis for implantable therapy.
h. **Lack of appropriate social support.** This is not an absolute exclusionary criteria but should be considered as the pain treatment team cannot assume all responsibility for the patient’s needs.
i. **Neurobehavioral cognitive deficits.** Severe cognitive impairments may interfere with the patient’s reasoning and judgment, making it difficult for them to assume the shared responsibility required for implantable therapy.

In summary, psychological testing serves as a screening tool to identify the appropriateness of invasive therapy for the management of chronic pain. Using the exclusionary criteria of Nelson
et al. (52), the psychological evaluation should focus on identifying these problems that may interfere with a successful outcome. As our medical judgment on the treatment of chronic pain is not infallible, neither is psychological screening. However, when the two are used together, better outcomes are more likely.

Screening trials

Although most clinicians recommend a screening trial prior to pump placement, a screening protocol that accurately predicts a successful outcome has not been established (53-55). In general, screening trials can be divided into the following: 1) single injection, 2) multiple injections, and 3) continuous infusion. There are no studies supporting one over the other, and the clinician should use their own judgment to decide which technique best suits their practice. It is recommended that the initial screening be done as an inpatient in a monitored setting. After 24 hours of observation, the patient may have the drug continuously infused in the comfort of their home. In a retrospective review of 429 physicians, 33.7% used a single intrathecal injection technique, 18.3% used a multiple injection with blinded placebo technique, and 35.3% used a continuous epidural infusion technique (56). Currently, the most common technique appears to be a continuous intrathecal infusion technique (57). The single injection technique involves a single administration of drug intrathecally or epidurally. The morphine dose is usually 0.5-1.0 mg intrathecally or 5-10 mg epidurally. An intrathecal or epidural equivalent of the patient’s daily systemic dose may also be used. The single injection technique has the advantages of low cost, low risks and ease. In addition, this technique probably overestimates side effects so in the absence of same, it is likely that the drug will be tolerated long term and at higher doses. Disadvantages are lack of correlation with a continuous infusion and higher placebo response. With the multiple injection technique, the patient is administered a series of injections, either intrathecally or epidurally. Morphine doses are similar for the single injection technique. Advantages of this technique are that the patients may receive a placebo injection for comparison with actual drug administration. A disadvantage is the lack of correlation with a continuous infusion. A continuous infusion may be administered intrathecally or epidurally through a temporary catheter connected to an external pump (58, 59). The response to therapy can be determined over days to weeks. The initial morphine dose is 20 μg/hour intrathecally or 200 μg/hour epidurally, or the equivalent to the patients daily systemic dose. The dose may be increased every 12-48 hours until pain relief or unacceptable side effects are reached. The advantage of this method is that it more closely mimics the implantable system. In addition, response to therapy can be more accurately assessed in the patient’s own environment, performing their normal daily activities. The single injection and multiple injections are performed in the clinic or hospital setting, making it difficult to accurately assess the patient’s response.

When performing the screening infusion trial, one would like to mimic the long-term delivery as closely as possible. Chronic daily infusion rates may range from as low as 0.1 ml/day (with SynchroMed pump) to 1.5 ml/day (with constant flow rate pumps). The lower limit of commonly used infusion pumps is 0.1 ml/hour which equals 2.4 ml/day. It is unclear if there is much difference in analgesic outcome with the same dose delivered as 0.1 ml/day versus 2.4 ml/day. However, preclinical pharmacokinetic studies have demonstrated that drug spread through the cerebrospinal fluid is volume-dependent. Therefore, a larger volume may result in a higher dermatomal spread of the drug, which may affect analgesia. This explains why some patients report excellent analgesia during the screening trial when higher volumes are infused,
only to find this pain relief disappear when the infusion pump is implanted and the same dose is infused at a lower volume. The best method to mimic chronic infusion therapy is with a microinfusion pump with a lower volume of 20 ml/hour. However, these infusion pumps are expensive, thus limiting their use.

**Drug selection chronic intrathecal therapy**

There is much uncertainty the decision-making process surrounding drug selection and dosing for chronic spinal drug delivery. According to an internet survey consisting of 413 physicians who represented management of 13,342 patients, responding physicians chose morphine most often, but many other drugs were selected without clear indications. There was evidence of wide variations in clinical practice among physicians who use this modality (60). This led to an interdisciplinary panel with extensive clinical experience in intraspinal infusion therapy who evaluated the results of the internet survey, the systematic reviews of the literature, and their own clinical experience. This panel proposed a scheme for the selection of drugs and doses for intraspinal therapy (61). They developed a hierarchy of therapeutic strategies which can be used during the screening process. Since the first polyanalgesic consensus meeting, the guidelines have been updated twice, in 2003 and 2007(62, 63).

To date, there are only two agents with U.S. Food and Drug Administration (FDA) approval for chronic spinal drug delivery to treat pain: morphine and ziconotide. Of the currently available drugs used for chronic spinal drug delivery, only ziconotide has been subjected to rigorous RCTs. The positive results of these trials led to FDA approval in 2004 (64-66). There is only one RCT comparing intraspinal drug delivery with conventional medical management in cancer pain. Two hundred and two cancer patients were randomized to intrathecal drug delivery (IDD) or comprehensive medical management (CMM). More IDD patients achieved success with significantly lower toxicity scores (67).

There are many complicating factors that should be weighed in determining the upper daily dose limit, or concentration. If one is limited to commercially available drugs, then there are limitations on drug concentrations. If patients require higher doses, then there will be frequent refills. The commercially available concentrations include: morphine, 50 mg/ml; ziconotide, 100 µg/ml; hydromorphone, 10 mg/ml; fentanyl and sufentanil, 50 µg/ml; Meperidine, 100 mg/ml; bupivacaine, 7.5 mg/ml; clonidine, 500 µg/ml; and, baclofen, 2000 µg/ml. The upper dose limit will depend on the availability of drug compounding. The goal is to try and keep the refill intervals between one and three months. However, there is growing concern over the development of catheter tip inflammatory masses (68). It has been suggested that the risk of granuloma formation is dependent upon the concentration of the drug delivered (69). The exact drug concentration that will predispose to granuloma formation is unknown; however, it is recommended that the lowest concentration possible be used.

With the development of the patient hand-held activator for bolus dosing, guidelines for drug selection and dosing may change drastically. However, it is too early to determine the impact of this technology on the selection process.

Intrathecal drug delivery is technically feasible, even for the long-term treatment of non-cancer pain. However, patient selection remains empiric and there are no long-term controlled studies to guide the overall placement of this therapy within the pain treatment armamentarium. Until more data emerge, this therapy will be reserved for that small group of patients whose pain is severe, limiting, and uncontrolled with more conservative measures.
Figure 1. The definition of low back pain. A. “Low back pain” is more precisely termed lumbosacral spinal pain, which encompasses both lumbar spinal pain (L) and sacral spinal pain (S). B. Radicular pain describes pain that is referred to the lower extremity and is caused by stimulation of a spinal nerve.

Figure 2. The functional spinal unit and the degenerative changes that lead to lumbosacral and radicular pain. A. The normal functional spinal unit. B. The degenerative changes leading to lumbosacral (disc disruption, facet joint arthropathy) pain and radicular pain (herniated nucleus pulposus). C. The degenerative changes of lumbar spondylosis leading to lumbosacral (facet joint) pain, radicular (foraminal stenosis) pain, and neurogenic claudication (central canal stenosis).
Table 1. Rational sequence for application of medical therapies in treating spinal pain, and level of evidence supporting each treatment. Level of evidence is based on the Oxford Evidence Based Medicine Levels for Treatment: Level I, high-quality RCTs or systematic reviews of RCTs; Level II, low-quality RCTs, cohort studies, or systematic reviews of cohort studies; Level III, case-control studies or systematic reviews of case-control studies; Level IV, case-series; Level V, expert opinion.

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<tr>
<th>Spinal Pain Type</th>
<th>Initial Therapy</th>
<th>Persistent Acute Pain</th>
<th>Persistent Chronic Pain</th>
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<td><strong>Acute Radicular Pain</strong></td>
<td>- Initial therapy: A 7-10 day course of an oral analgesic (NSAID or acetaminophen, ± opioid analgesic) with a muscle relaxant, for those with superimposed muscle spasm. (Level I) (70)</td>
<td>- Persistent acute radicular pain: Between 2 and 6 weeks following onset of acute radicular pain, consider lumbar epidural steroid injection to speed resolution of radicular symptoms (Level II) (71)</td>
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<tr>
<td><strong>Chronic Radicular Pain</strong></td>
<td>- Initial therapy: Tricyclic antidepressants (TCAs; e.g., nortriptyline, desipramine) and newer serotonin norepinephrine reuptake inhibitors (SNRIs; e.g., venlafaxine, duloxetine) are effective in the treatment of neuropathic pain. Antiepileptic drugs (e.g., gabapentin, pregabalin) also treat neuropathic pain effectively (Level I). (18) - Chronic radicular pain may respond to treatment with chronic opioids, but neuropathic pain is less responsive to opioids than nociceptive pain. (Level II) (72, 73)</td>
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<td><strong>Acute Lumbosacral Pain</strong></td>
<td>- Initial therapy: A 7-10 day course of an oral analgesic (NSAID or acetaminophen, ± opioid analgesic) with a muscle relaxant, for those with superimposed muscle spasm. (Level I) (70)</td>
<td>- Persistent acute lumbosacral pain: Between 2 and 6 weeks following onset of chronic radicular pain, consider referral for physical therapy for stretching, strengthening, and aerobic exercise in conjunction with patient education. (Level I) (74)</td>
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<tr>
<td><strong>Chronic Lumbosacral Pain</strong></td>
<td>- Initial therapy: Consider diagnostic medial branch blocks of the nerves to the facet joints. If there is &gt;50% pain relief with the diagnostic blocks, consider radiofrequency treatment. (Level II) (26)</td>
<td>- Persistent chronic lumbosacral pain: Consider enrollment in a formal multidisciplinary pain program that incorporates medical management, behavioral therapy, and physical therapy. (Level I) (75) - Consider cognitive-behavioral therapy. (Level I) (76) - If no response to diagnostic facet blocks and the there is MRI evidence of early degenerative disc disease affecting less than two intervertebral discs, consider diagnostic provocative discography. (Level III) (29) If discography is concordant (pain is reproduced at anatomically abnormal level(s) and there is no pain at an adjacent anatomically normal level), consider treatment with intradiscal electrothermal therapy (IDET) at the symptomatic level(s). (Level II) (33)</td>
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References


45. Brandwin MA, Kewman DG.


RISK OF BLEEDING COMPLICATIONS AFTER PAIN PROCEDURES IN ANTICOAGULATED PATIENTS

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Introduction

Although mostly minimally invasive, pain treatment procedures bear an inherent risk of excessive bleeding and nerve damage. This concern is heightened when patient’s clotting mechanism is impaired, particularly in the setting of neuraxial procedures involving epidural and intrathecal space. Spinal hematomas resulting from spinal or epidural puncture are rare, but their neurological sequela can be severe. Fortunately, these events are uncommon and difficult to approach with prospective studies. Current guidelines for neuraxial procedures in the setting of anticoagulation as created by American Society of Regional Anesthesia (ASRA) are based on mostly retrospective reviews, case reports, and laboratory studies. Excessive hemorrhage from peripheral analgesia procedures is also uncommon; and these cases typically do not progress to long-term neurological damage.

The most feared coagulation complication following epidural or intrathecal puncture is spinal hematoma. These events are rare and their commonly quoted estimated incidence is less than 1:150000 and 1:220000 after epidural and spinal procedures, respectively (Tryba 1993). However, more recent epidemiologic surveys as reported in the ASRA 2010 Practice Advisory suggest the frequency of neurologic dysfunction resulting from hemorrhagic complications associated with neuraxial blockade is as high as 1 in 3000 in some patient populations. In a retrospective review Vandermeulen and coworkers have compiled a total 61 cases of spinal hematoma following neuroaxial procedures that were reported during throughout the 20th century (Vandermeulen, Van Aken et al. 1994). Of these, 15 patients had spinal and 46 had epidural punctures. Hemostatic abnormalities were present in 42 patients. These included heparin, antiplatelet agents (NSAIDs, ticlopidine). Difficulty in placing the needle was encountered in 15 patients and blood through the needle was present in 15 patients.

In all the instances of spinal hematoma the presenting symptoms were neurological, typically progressive motor or sensory deficits, and occasionally bowel and bladder dysfunction. Prompt diagnosis and surgical decompression appear to be crucial in treatment of spinal hematoma. Although the neurological symptoms may resolve even without the treatment, the patients who have undergone decompression with 8 hours of onset of the symptoms were much more likely to have complete or partial return of function than other patients (Vandermeulen, Van Aken et al. 1994).
Spinal cord injuries were the leading cause of claims in the American Society of Anesthesiologists (ASA) Closed Claims database involving claims related to nerve injury associated with general or regional block from 1990-1999. Spinal hematomas accounted for nearly half of these spinal cord injuries. Analysis of ASA closed claims related to nerve injury after regional anesthesia between 1980 and 1999 included 1005 regional anesthesia claims, 84 of which were related to neuroaxial nerve injury. Of these, 36 (43%) were due to spinal hematoma. 26 (72%) of the hematoma cases were due to coagulopathy: Intrinsic coagulopathy (dysfunction in clotting or fibrinolytic cascade) was present in 2 patients. 20 patients have received intraoperative heparin and 2 patients were on low molecular weight heparin. 3 patients were on concomitant antiplatelet therapy and subcutaneous heparin. The symptoms typically occurred during the first postoperative day and were diagnosed the next day. Increased motor and sensory blocks were present in 30 and 21 patients respectively. Only 9 patients complained of back pain.

Changes in coagulative, fibrinolytic and thrombolytic mechanisms escalate the risk of spinal hematoma formation as well peripheral tissue bleeding following regional anesthesia and pain procedures. Coagulopathy can be caused by numerous intrinsic processes and disease states manifest by platelet disorders, clotting factor abnormalities or disseminated intravascular coagulation. Such conditions include inherited coagulopathies, uremia and impaired liver synthetic activity. Drug induced coagulopathy is an increasingly common condition due to popularity of anticoagulant, fibrinolytic and thrombolytic therapies. Increased risk of bleeding in an anticoagulated patient is well-recognized. The list of medications affecting coagulation and clot dissolution is extensive. The risks bleeding that these drugs pose following invasive procedures and corresponding safety recommendation are explored extensively in recent American Society of Regional Anesthesia (ASRA) guidelines (Horlocker, Wedel et al. 2010), and are summarized herein.

Specific agents

Warfarin

Warfarin is widely used oral anticoagulant. It inhibits the synthesis of vitamin K dependent coagulation factors II, VII, IX, and X and anticoagulant proteins C and S (GSM 2003). Warfarin is used extensively for prophylaxis and treatment of deep vein thrombosis and pulmonary embolism, and thromboembolism prophylaxis in patients with mechanical prosthetic heart valves or atrial fibrillation. Decrease in factors VII and X is reflected by an increase in prothrombin time (PT) and, correspondingly, the International Normalized Ratio (INR). Therapeutic range of warfarin is typically at INR between 2 and 3. After warfarin is discontinued it takes approximately 4 days to return to normal coagulation status. Abnormalities in hemostasis typically do not occur at the clotting factors levels above 40%. At these levels the INR is measured at 1.4. It is thus presumed that coagulation status is normal in patients with INR less then 1.5. Accordingly, the placement of epidural or spinal needle, and removal of a catheter in patient anticoagulated with warfarin is safe only if the INR less then 1.5. This applies only to patients who are or have just discontinued warfarin, and who do not have additional risks for coagulopathy, iatrogenic or due to disease processes. If patients are concomitantly taking other
anticoagulant or suffer from coagulopathogenic conditions their risk for development of spinal hematoma is increased.

Anticoagulation produced by warfarin can be rapidly reversed in an emergency by administration of fresh frozen plasma (FFP) or vitamin K.

**Recommendations for Management of the Patient on Oral Anticoagulants:**

1. Caution should be used when performing neuraxial techniques in patients recently discontinued from long-term warfarin. In the first 1 to 3 days after discontinuation of warfarin therapy, the coagulation status may not be adequate for hemostasis despite a decrease in the INR. The anticoagulant therapy must be stopped (ideally 4-5 days before the planned procedure) and the INR must be normalized before initiation of neuraxial block.

2. Avoid concurrent use of medications that affect other components of the clotting mechanisms and may increase the risk of bleeding complications without influencing the INR (aspirin, NSAIDs, ticlopidine and clopidogrel, UFH, LMWH).

3. In patients receiving an initial dose of warfarin before surgery, we suggest that the INR should be checked before neuraxial block if the first dose was given more than 24 hrs earlier or if a second dose of oral anticoagulant has been administered.

4. In patients receiving low-dose warfarin therapy during epidural analgesia, we suggest that their INR be monitored on a daily basis.

5. Neurologic testing should be performed routinely during epidural analgesia for patients on warfarin therapy. The type of analgesic solution be tailored to minimize the degree of sensory and motor blockade.

6. As thromboprophylaxis with warfarin is initiated, neuraxial catheters should be removed when the INR is < 1.5. Neurologic assessment should be continued for at least 24 hrs after catheter removal.

7. In patients with INR 1.5 - 3, removal of indwelling catheters should be done with caution and the medication record reviewed for other medications that may influence hemostasis that may not effect the INR (NSAIDs, ASA, clopidogrel, ticlopidine, UFH, LMWH). Neurologic status should assessed before catheter removal and continued until the INR has stabilized at the desired prophylaxis level.

8. In patients with an INR > 3, warfarin dose should be held or reduced in patients with indwelling neuraxial catheters.

**Heparin**

Heparin is a glycosaminoglycan composed of variable-length chains. The unfractionated and fractionated low molecular weight forms differ in duration of action and relative activity at the substrates along the coagulation cascade. In general heparin accelerates the inactivation of factors IXa, Xa and IIa (thrombin) by antithrombin III (ATIII). When ATIII is bound to larger heparin molecules, it has strong affinity to factor II, whereas ATIII-low molecular weight heparin complexes primarily inactive factor Xa. Heparin may also interfere with platelet aggregation, but this happens only at doses higher than therapeutic. The anticoagulant effect of heparin is both dose dependent and is not linear but increases disproportionately with increasing
doses. Intravenous heparin administration has an immediate anticoagulant effect. Effect of intravenously administered unfractionated heparin on coagulation is monitored with aPTT. Therapeutic anticoagulation with intravenous heparin usually requires that aPTT be maintained at 1.5 to 2.0 the normal value. In these patients coagulation state is abnormal and they are at increased risk for spinal hematoma after neuroaxial procedure. Patients who are receiving IV heparin should discontinue this medication for at least 2 and preferably 4 hours prior to scheduled procedure and their coagulation status should then be checked. This principle also applies to removal of indwelling catheters. Following the procedure motor and sensory function of lower extremities should be monitored for at least 12 hours.

Considerations for starting heparinization after neuroaxial procedure should depend on whether it was associated with blood through the needle or traumatic needle placement. On one hand, if the procedure was uneventful, then heparinization can be started after 60 minutes. But, if the procedure was complicated by bloody tap or traumatic needle placement, then the patient is at a higher risk for spinal hematoma. In these patients the risks and benefits of anticoagulation should be weighed, and it may be prudent to postpone heparinization for 24 hours after the procedure.

Subcutaneous administration has a 1-2 hour delay in anticoagulation. Subcutaneously (SQ) administered small-dose (5000 U) heparin for prophylaxis doesn’t raise the aPTT in the majority of patients, and it rarely exceeds 1.5 the normal value. The risk of developing spinal hematoma in patients receiving SQ low-dose heparin is considered very low, and only a few such cases were reported. Its SQ use is therefore not viewed as a contraindication for neuroaxial procedure according to ASRA guidelines. However, in the elective outpatient setting, where patients are typically monitored for less than one hour after the procedure and it may be prudent to not to perform neuroaxial procedure while patient is receiving SQ heparin.

Patients who have been receiving SQ or IV heparin for several days may develop heparin-induced thrombocytopenia with ensuing coagulopathy. It is therefore advised that the platelet count be measured in these patients prior to performing neuroaxial procedure even after heparin has been discontinued.

**Recommendations for Management in setting of UFH:**

1. Review of the patient’s medical record for concurrent use of medications that affect other components of the clotting mechanisms (antiplatelet medications, LMWH, oral anticoagulants).

2. In patients receiving prophylaxis with subcutaneous UFH with dosing regimens of 5000 U twice daily, there is no contraindication to the use of neuraxial techniques. The risk of neuraxial bleeding may be reduced by delay of the heparin injection until after the block and may be increased in debilitated patients after prolonged therapy.

3. The safety of neuraxial blockade in patients receiving doses greater than 10,000 U of UFH daily or more than twice daily dosing of UFH has not been established. Although the use of thrice-daily UFH may lead to an increased risk of surgical-related bleeding, it is unclear whether there is an increased risk of spinal hematoma. We suggest that the risk and benefits of thrice-daily UFH be assessed on an individual basis and that techniques to facilitate detection of new/progressive
neurodeficits (eg, enhanced neurologic monitoring occur and neuraxial solutions to minimize sensory and motor block).

4. Patients receiving heparin for more than 4 days have a platelet count assessed before neuraxial block and catheter removal for HIT.

5. Combining neuraxial techniques with intraoperative anticoagulation with heparin during vascular surgery is acceptable with the following recommendations:
   - Avoid the technique in patients with other coagulopathies.
   - Delay heparin administration for 1 hr after needle placement.
   - Remove indwelling neuraxial catheters 2 to 4 hrs after the last heparin dose and assess the patient’s coagulation status; re-heparin 1 hr after catheter removal.
   - Monitor the patient postoperatively to provide early detection of motor blockade and consider use of minimal concentration of local anesthetics to enhance the early detection of a spinal hematoma.

Low molecular weight heparin (LMWH) differs from the unfractionated heparin by longer half-life and stronger activity at factor Xa substrate. When used for thromboprophylaxis LMWH is typically administered twice daily in the US, whereas once-a-day administration is common in Europe. Closed claims analysis of injuries related to regional anesthesia during the 1980’s and 1990’s showed that hematoma accounted 43% of neuroaxial anesthesia claims, many of these were associated with LMWH heparin use (Lee, Posner et al. 2004). Monitoring of coagulation status of patients receiving LMWH is difficult. Clotting or bleeding times do not reflect the degree of anticoagulation. Although factor Xa is the principal substrate for inactivation by LMWH-bound ATIII, measurement of anti Xa level doesn’t correlate well with risk of bleeding. Because of lack of monitoring techniques, anticoagulation produced by LMWH is estimated based on time elapsed since last injection. In patients who are receiving standard doses of LMWH for thromboprophylaxis, the current guidelines dictate that neuroaxial procedure be performed not sooner than 10 to 12 hours after last LMWH dose. This time interval should be at least 24 hours in patient who are therapeutically anticoagulated with higher doses of LMWH.

If the neuroaxial procedure was free from blood through needle or catheter, then a dose LMWH can be given 2 hours after the procedure. This time interval should be increased to 24 hours if the puncture was bloody or traumatic. Decisions on retention and removal of indwelling neuroaxial catheter should depend on the mode of administration of LMWH. In patients who are receiving a once-a-day prophylactic regimen of LMWH, the catheter may be retained and removed 10 to 12 hours after last LMWH dose. If the LMWH regimen consists of twice-a-day dosing then the catheter should be removed prior to first LMWH dose.

Recommendations for Management in setting of LMWH:

1. Initiation of LMWH therapy after presence of blood during needle and catheter placement should be delayed for 24 hrs
2. In patients on preoperative LMWH thromboprophylaxis needle placement should occur at least 10 to 12 hrs after the LMWH dose
3. In patients receiving higher (treatment) doses of LMWH (enoxaparin 1 mg/kg every 12 hrs, enoxaparin 1.5 mg/kg daily, dalteparin 120 U/kg every 12 hrs, dalteparin 200
U/kg daily, or tinzaparin 175 U/kg daily) delay of at least 24 hrs before needle insertion.

4. In patients administered a dose of LMWH 2 hrs preoperatively (general surgery patients), we recommend against neuraxial techniques because needle placement would occur during peak anticoagulant activity.

5. Twice-daily dosing is associated with an increased risk of spinal hematoma. The first dose of LMWH should be administered no earlier than 24 hrs after needle insertion. Indwelling catheters should be removed before initiation of LMWH thromboprophylaxis. Administration of LMWH should be delayed for 2 hrs after catheter removal.

6. Single-daily dosing, the first postoperative LMWH dose should be administered 6 to 8 hrs after procedure. The second postoperative dose should occur no sooner than 24 hrs after the first dose. Indwelling neuraxial catheters may be safely maintained and should be removed a minimum of 10 to 12 hrs after the last dose of LMWH. Subsequent LMWH dosing should occur a minimum of 2 hrs after catheter removal. No additional hemostasis-altering medications should be administered due to the additive effects.

Antiplatelet drugs

Platelet activity inhibition can be achieved by several mechanisms. Non-steroidal anti-inflammatory medications (NSAIDs) inhibit the activity of cyclooxygenase enzyme complex with resultant decreased production of inflammatory mediators as well as thromboxane. Clopidogrel (Plavix) and, now rarely used, ticlopidine (Ticlid) inhibit ADP-induced platelet-fibrinogen binding and platelet aggregation. Clopidogrel is increasingly used for prophylaxis for thromboembolic events, particularly to prevent coronary artery stent occlusion. Another group of antiplatelet medications interfere with the GP IIb/IIIa receptors, thereby inhibiting platelet-fibrinogen and platelet-von Willebrand factor binding. Examples of drugs in this class are abciximab (Reopro), eptifibatide (Integrilin) and tirofiban (Aggrastat).

Safety of neuroaxial procedure in patients receiving NSAIDs remains controversial and practical approaches to this issue vary. In principle, some degree of anticoagulation is expected in patients who are receiving even low dose of NSAIDs. Empirical evidence, however, suggests that NSAIDs increase the risk for bleeding from neuroaxial puncture is only slightly (1:150000 vs 1:220000 for epidural, and 1:220000 vs 1:320000 for intrathecal procedures (Stafford-Smith 1996)). The use of NSAIDs is widespread. At the same time very few cases of spinal hematoma in patients receiving NSAIDs without other anticoagulants were reported. Based on this and other evidence the ASRA guidelines suggest that “NSAIDs appear to represent no added significant risk for the development of spinal hematoma in patients having epidural or spinal anesthesia. The use of NSAIDs alone does not create a level of risk that will interfere with the performance of neuraxial blocks.” Although the guidelines do not recommend discontinuing NSAIDs prior to neuroaxial procedure, the potential anticoagulant effect of NSAIDs is well-recognized. Because of the concerns for increased risk of bleeding in these patients, more conservative approach is commonly practiced by requiring discontinuation of the NSAIDs before procedures. Only aspirin and indomethacin inhibit platelet cyclooxygenase activity irreversibly, whereas other NSAIDs’ action on the platelets is reversible. In order to eliminate the
The anticoagulation effect of these drugs, it is accordingly recommended that aspirin be discontinued 7 days and other NSAIDs 4 days prior to the scheduled procedure.

Little data is available on the risk of spinal hematoma in patients receiving ticlopidine or clopidogrel. Although these drugs are relatively new, 3 spinal hematomas after neuroaxial procedures as well as severe bleeding after lumbar sympathetic block have so far been reported. The majority of reports of perioperative bleeding in presence of these drugs were after surgeries and endovascular procedures. These experiences, as well as the manufacturers’ recommendations, formed the basis for current ASRA guidelines: patients should discontinue clopidogrel at least 7 days before the scheduled procedure.

GP IIb/IIIa inhibitors are typically administered parenterally for thrombolysis during acute coronary syndrome. Platelet activity in these patients returns to normal 24 to 48 hours after administration of abciximab and 4 to 8 hours after eptifibatide and tirofiban. Accordingly neuroaxial procedure should be delayed until platelet activity has normalized.

Bleeding time is often employed to assess coagulation status in patients receiving antiplatelet medications. This test however does not reliably predict coagulation status in these patients. It is particularly unreliable in assessing positive predictive value for post-operative bleeding in anticoagulated patients (Gewirtz, Kottke-Marchant et al. 1995).

Recommendations for the Patient Receiving Antiplatelet Medications:

1. Nonsteroidal anti-inflammatory drugs seem to represent no added significant risk for the development of spinal hematoma in patients having epidural or spinal anesthesia.
2. In patients receiving NSAIDS, avoid neuraxial techniques if the concurrent use of other medications affecting clotting mechanisms, such as oral anticoagulants, UFH, and LMWH, is anticipated in the early postoperative period because of the increased risk of bleeding complications.
3. COX-2 inhibitors have minimal effect on platelet function
4. Neuraxial blockade should be delayed after the discontinuation of ticlopidine is 14 days. Neuraxial blockade should be delayed 7 days after discontinuation of clopidogrel. If a neuraxial block is indicated between 5 and 7 days of discontinuation of clopidogrel, normalization of platelet function should be documented.
5. After administration, the time to normal platelet aggregation is 24 to 48 hrs for abciximab and 4 to 8 hrs for eptifibatide and tirofiban. Neuraxial techniques should be avoided until platelet function has recovered. Should a GP IIb/IIIa antagonists (abciximab, eptifibatide, tirofiban) be administered after a neuraxial technique the patient should be carefully monitored neurologically?
Other agents

Thrombolytic Therapy
Streptokinase and Urokinase: The majority of case reports involve spontaneous epidural hematoma following administration of thrombolytic therapy. As of the 2010 ASRA Practice Advisory on Regional Anesthesia in the Patient Receiving Antithrombotic or Thrombolytic Therapy, there were 6 cases of spinal hematoma involving the concomitant use of neuraxial anesthesia and fibrinolytic/thrombolytic therapy.

Recommendations:
1. Avoid thrombolytic drugs for 10 days after puncture of noncompressible vessels (including epidural veins)
2. In patients who have received fibrinolytic and thrombolytic drugs, we recommend against performance of spinal or epidural anesthetics except in highly unusual circumstances. Data are not available to clearly outline the length of time neuraxial puncture should be avoided after discontinuation of these drugs.
3. In those patients who have received neuraxial blocks at or near the time of fibrinolytic and thrombolytic therapy, we recommend that neurological monitoring should be continued with a maximum of 2 hours between neurologic checks. If ongoing epidural catheter infusion is combined with fibrinolytic and thrombolytic therapy, the infusion should be limited to drugs minimizing sensory and motor block to facilitate assessment of neurologic function.
4. There is no definitive recommendation for removal of neuraxial catheters in patients who unexpectedly receive fibrinolytic and thrombolytic therapy during a neuraxial catheter infusion. ASRA suggests measuring fibrinogen level (one of the last clotting factors to recover) to evaluate the presence of residual thrombolytic effect and appropriate timing of catheter removal.

New Anticoagulants

Thrombin Inhibitors (Desirudin, Lepirudin, Bivalirudin, and Argatroban)
Recombinant hirudin derivatives, including desirudin (Revasc), lepirudin (Refudan), and bivalirudin (Angiomax) inhibit both free and clot-bound thrombin. Argatroban (Acova), an L-arginine derivative has a similar mechanism of action. These medications are typically used for the prevention of thrombosis in patients with heparin-induced thrombocytopenia. The anticoagulant effect of thrombin inhibitors is monitored by the aPTT and is present for 1 to 3 hrs after intravenous administration. The antithrombin effect cannot be reversed pharmacologically.

Recommendations for Patients Receiving Thrombin Inhibitors (Desirudin, Lepirudin, Bivalirudin, and Argatroban)
1. In patients receiving thrombin inhibitors, ASRA recommends AGAINST the performance of neuraxial techniques
**Fondaparinux (Arixtra)** is the first in new synthetic pentasaccharide anticoagulant that selectively inhibits factor Xa via antithrombin-dependent actions (GSM 2003). It does not inhibit thrombin (factor IIa). Fondaparinux is typically used in acute setting for thromboembolism prophylaxis after lower extremity orthopedic surgery. Its plasma half-life is approximately 18 hours (in comparison that of enoxaparin (Lovenox) is 6 to 7 hours). During clinical study involving neuroaxial blockade and postoperative fondaparinux use a single case of spinal hematoma was reported. The dose of fondaparinux administered during in that case was twice the currently recommended therapeutic dose. During trials the subjects received fondaparinux only if the needle and catheter were placed atraumatically on the first attempt. The catheters were removed 2 hours before the first fondaparinux dose.

Clinical experience with this relatively new drug is still limited and the actual risk of spinal hematoma is unknown. Accordingly, current guidelines call for not diverging from the protocol used during clinical trials: avoid using fondaparinux unless the needle placement required only one pass and was atraumatic, remove indwelling catheter at least 2 hours before the first dose. The minimum safe time interval between the last fondaparinux dose and neuroaxial procedure is unknown. Decision under these circumstances requires clinical judgment with the consideration that the half-life of fondaparinux is about 3 times that of enoxaparin.

**Recommendations for the Patient Receiving Fondaparinux:**

1. Performance of neuraxial techniques should occur under conditions used in clinical trials (single-needle pass, atraumatic needle placement, avoidance of indwelling neuraxial catheters).

**Dabigatran Etexilate** and **Rivaroxaban** are new oral medications in phase 3 clinical trials in the United States (and already released for use in Canada and Europe) that are intended for use as thromboprophylaxis after total knee and/or hip replacement. These anticoagulants inhibit thrombin and factor Xa. Dabigatran etexilate is a prodrug that specifically and reversibly inhibits both free and clot-bound thrombin. Plasma levels peak at 2 hrs. The half-life is 8 hrs after a single dose and up to 17 hrs after multiple doses. Dabigatran etexilate prolongs the aPTT, but its effect is not linear and reaches a plateau at higher doses. However, the ecarin clotting time and thrombin time are particularly sensitive and display a linear dose-response at therapeutic concentrations.

Rivaroxaban is a potent selective and reversible oral activated factor Xa inhibitor, with a maximum inhibitory effect 1 to 4 hrs after administration. Inhibition is maintained for 12 hrs. The antithrombotic effect may be monitored with the PT, aPTT, and Heptest, all of which demonstrate linear dose effects. The terminal elimination half-life is 9 hrs in healthy volunteers and may be prolonged to 13 hrs in the elderly owing to a decline in renal function. Although there have been no reported spinal hematomas with Dabigatran Etexilate or Rivaroxaban, the lack of information regarding the specifics of block performance and the prolonged half-life warrants a cautious approach.

**Herbal medications and supplements:**
Recent surge in popularity of herbal medications sold as dietary supplements has also given rise to the concern for their potential adverse side effects. Several over-the-counter supplements,
vitamin E, garlic, ginkgo, and ginseng, are known to alter the clotting mechanisms and potentially be responsible for increased risk of bleeding.

Garlic in a variety of forms is used extensively to improve cholesterol metabolism and reduce blood pressure. It reportedly inhibits in vivo platelet aggregation and may potentiate the effect of other platelet inhibiting drugs. There are no reported bleeding complications from procedures on patients who are using garlic therapy. One case of epidural hematoma in heavy garlic user was reported, however in this case the hematoma occurred spontaneously in an elderly patient.

Ginkgo biloba extract is popular dietary supplement used to enhance memory, treat dementia and organic brain syndrome. Some of the active compounds in the extract competitively inhibit platelet activating factors. No bleeding complications from procedures on patients treated with ginkgo biloba have so far been reported. There are however 4 reports of spontaneous intracranial bleeding attributed to ginkgo biloba use.

Ginseng dietary supplement represents several species of plants native to Asia and North America. It is allegedly beneficial for many health conditions, including lowering of blood glucose level in diabetes, protection against stress and restoration of immune system. Ginseng exerts its anticoagulant properties by inhibiting thromboxane formation. Its anticoagulant activity in humans has not yet been shown; however, when warfarin and ginseng are used concomitantly, the anticoagulant activity of warfarin may be reduced.

Vitamin E is lipid soluble vitamin found in many foods. Its antioxidant properties and yet-to-be-proven beneficial effects in cardiovascular disease have resulted in widespread high-dose use. At high doses vitamin E exhibits activity antagonistic to vitamin K, and possibly inhibits platelet activation. In humans it was shown to increase gingival bleeding at moderate doses, particularly in combination with aspirin (Liede, Haukka et al. 1998). There are no reports of spinal hematoma after neuraxial procedure in patients who were receiving vitamin E without other anticoagulants. Dietary supplements, ginkgo biloba, garlic and ginseng do not appear alter the risk of spinal hematoma. Accordingly there is no need to discontinue these medications before planned neuraxial procedure. ASRA guidelines do not address safety and risks of hematoma with of vitamin E. Although no adverse events after neuraxial procedure attributable to vitamin E have been reported, its anticoagulant effect is exerted by two mechanisms. Therefore, it may be prudent to require that patients discontinue this medication for 4 days before the scheduled procedure. Such practice may be particularly applicable in patients receiving high dose of this medication.

These recommendations do not apply to the patients who concurrently use other agents that may alter their coagulation status. In these patients the risk for spinal hematoma is unknown and could be elevated.

**Management of the Patient Receiving Herbal Therapy:**
Herbal drugs, by themselves, seem to represent no added significant risk for the development of spinal hematoma in patients having epidural or spinal anesthesia.
Herbal Medications with the Greatest Impact on Hemostasis:

<table>
<thead>
<tr>
<th>Herb</th>
<th>Effects</th>
<th>Time to normal hemostasis after discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garlic</td>
<td>Inhibition of platelet aggregation</td>
<td>7 d</td>
</tr>
<tr>
<td></td>
<td>Increased fibrinolysis</td>
<td></td>
</tr>
<tr>
<td>Ginkgo</td>
<td>Inhibition of platelet-activating factor</td>
<td>36 hrs</td>
</tr>
<tr>
<td>Ginseng</td>
<td>Increased prothrombin and aPPTs</td>
<td>24 hrs</td>
</tr>
</tbody>
</table>

Peripheral procedures

Bleeding complications that result in most severe and permanent sequela tend to be due to spinal hematomas after neuraxial procedures. Cases of excessive bleeding resulting from peripheral blocks are also occasionally reported, however their incidence and relative risks with anticoagulation are poorly studied. Bleeding complications appear to be relatively common after vascular procedures. For example, femoral artery hematomas associated with cardiovascular angiography are described at a rate of 22%, and 6% of the hematomas are greater than 5 cm (Berry, Kelly et al. 2004). Patients in these procedures typically receive anticoagulation therapy. Most of the information about bleeding stemming from peripheral blocks is derived from case reports. The bleeding can be extensive particularly in the retroperitoneal space after psoas compartment and lumbar sympathetic plexus blocks. Vascular injury and bleeding may be associated with neurological deficits; however these tend to resolve completely within 12 months. The information on the risk of increased bleeding in anticoagulated patients undergoing peripheral blocks is limited. Until more is known about these risks, the ASRA consensus guidelines conservatively apply the recommendations for the neuroaxial procedures to peripheral blocks.

Spinal hematomas and the ensuing neurological damage are probably the most serious complications of regional pain procedures. The risk of spinal hematomas increases with anticoagulant medications use. The practice guidelines intended to reduce these risks are summarized in Table 1. The guidelines are based on past experience, formal studies and laboratory data. These guidelines do not encompass the variety of individual circumstances and often clinician’s assessment and judgment will be ultimately decisive. For example, if a patient is on low dose aspirin, but reports easily bruised skin, then ASRA recommendation regarding NSAIDs and neuroaxial procedures may not apply and the clinician may prudently require that patient discontinues aspirin. Most important is the issue of increasingly common concomitant use of more than one anticoagulant agent. Examples for such combined therapy are aspirin and clopidogrel, or vitamin E and LMWH. Patients on such therapies are probably at increased risk for bleeding compared to that with a single anticoagulant. However, no rational guidelines can be made at this point, and these circumstances will require clinician’s judgment.

Recommendations for Management of the Patient Undergoing Plexus or Peripheral Block:
1. For patients undergoing deep plexus or peripheral block, ASRA recommends that recommendations regarding neuraxial techniques be similarly applied
References


**Table 1: Summary of guidelines for neuroaxial procedures in anticoagulated patients**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Monitoring</th>
<th>Needle placement</th>
<th>Catheter removal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>INR &lt; 1.5 is required for both needle placement and removal</td>
<td>Discontinue for 5 days before procedure, check INR</td>
<td>Check INR, remove catheter if INR &lt; 1.5</td>
</tr>
<tr>
<td>Unfractionated heparin, low-dose subcutaneous</td>
<td>PTT is not required</td>
<td>Discontinuation of heparin is not required; however consider stopping heparin for outpatient procedure. Consider thrombocytopenia if prolonged use</td>
<td>Discontinuation of heparin is not required. Consider thrombocytopenia if prolonged use</td>
</tr>
<tr>
<td>Unfractionated heparin, IV therapeutic dose</td>
<td>Monitor PTT</td>
<td>Discontinue heparin 2-4 hours before procedure; then check PTT. May restart heparin 1 hour after procedure. Consider delaying for 24 hour if bloody tap. Monitor for neurological deficits</td>
<td>Discontinue heparin 2-4 hours before removing catheter, then check PTT. May restart heparin 1 hour after catheter removal. Monitor for neurological deficits</td>
</tr>
<tr>
<td>Low molecular weight heparin</td>
<td>Anti-factor Xa monitoring is not useful</td>
<td>Discontinue LMWH 10-12 hours before procedure. If high-dose thrombolytic therapy then 24 hours. Restart LMWH 2 hours after procedure. Consider delaying for 24 hours if bloody or traumatic needle placement</td>
<td>Discontinue LMWH 10-12 hours before procedure. If high-dose thrombolytic therapy then 24 hours. Restart LMWH 2 hours after procedure. Consider delaying for 24 hours if bloody or traumatic needle placement</td>
</tr>
<tr>
<td>Antiplatelet drugs: NSAIDs</td>
<td>Bleeding time is not predictive</td>
<td>Discontinuation of NSAIDs not required. Some practices discontinue aspirin 7 days and other NSAIDs 4 days before procedure</td>
<td>Discontinuation of NSAIDs not required. Some practices discontinue aspirin 7 days and other NSAIDs 4 days before procedure</td>
</tr>
<tr>
<td>Antiplatelet drugs: ADP inhibitors</td>
<td>Bleeding time is not predictive</td>
<td>Discontinue clopidogrel for 7 days</td>
<td>Catheter should be removed before starting antiocoagulation</td>
</tr>
<tr>
<td>Antiplatelet drugs: GP IIb/IIIa inhibitors</td>
<td>Bleeding time is not predictive</td>
<td>Refer to manufacturer’s insert for guidelines. Platelet activity needs to be normalized: Abciximab – 24 to 48 hours. Eptifibatide and tirofiban – 4 to 8 hours.</td>
<td>Catheter should be removed before starting thrombolysis</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>Undetermined</td>
<td></td>
<td>Remove catheter 2 hours before first fondaparinux dose. Don’t start fondaparinux if bloody or traumatic needle placement</td>
</tr>
<tr>
<td>Supplements and herbal medications: Vitamin E, ginkgo, garlic, ginseng</td>
<td>PT, PTT may be elevated with high dose vitamin E</td>
<td>Discontinuation is not required. Some practices discontinue high dose vitamin E before procedure</td>
<td>Discontinuation is not required</td>
</tr>
</tbody>
</table>
ACUTE PAIN MECHANISMS

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When stimuli threaten the homeostatic integrity of tissue, either directly or indirectly by disrupting the vasculature, typically autonomic (changes in blood pressure and heart rate) and/or hormonal (adrenal and pituitary secretion) responses are generated as well as the subjective sensation of pain. These stereotypical responses are for the most part independent of the modality and source of the insult. This article discusses several of the components of the physiology and pharmacology involved in the generation of the acute pain state. Emphasis is placed on the primary afferent fiber and spinal elements as the properties of these linkages provide useful insights into the pain state generated by tissue injury stimuli as exemplified by post-operative pain.

PERIPHERAL ELEMENTS

Nociceptors

Receptors transduce energy of a specific modality into generator and then action potentials. Nociceptors, frequently called “free nerve endings” are unencapsulated nerve endings that are activated in response to stimuli that threaten or actually produce tissue damage. Some respond exclusively to one modality e.g. chemical or noxious heat, others are sensitive to several varieties of noxious stimulation (polymodal nociceptors). Virtually all nociceptors are innervated by a subpopulation of small-diameter myelinated (Aδ) and unmyelinated (C) nerve fibers. Although these free nerve endings have no attached structural receptor, other peripheral components of nociceptive sensory integration are located in the surrounding tissue. Terminals of both Aδ and C fibers are bare of myelin for 100 to 400 μm, these endings are juxtaposed with small blood vessels and mast cells [32]. This triad, along with other nearby nerve terminals is thought to operate as a functional unit. Antidromic activation of peripheral terminals, which can be initiated by tissue injury, releases neurotransmitters in the periphery, including substance P (SP) and glutamate. Tissue injury can also result in increased local concentrations of arachadonic acid metabolites (prostaglandins and leukotrienes). These agents can either directly activate other C fibers (which have been shown to have both neurokinin [7] and excitatory amino acid (EAA) receptors [11], degranulate mast cells and/or lead to plasma extravasation and perhaps edema [83]. Substances released from mast cells (e.g. histamine or cytokines) or the vasculature can cause subsequent activation or sensitization of the nociceptors. Activated platelets, for example, are known to be involved in peripheral sensitization [66]. Additional sensitizing agents and their endogenous sources are detailed in Table I. Together, agents from this variety of sources produce receptor sensitization as well as ongoing discharge of afferent nociceptive nerve fibers. Thus, nociceptive terminals use chemical products from other cells to transduce real or impending tissue damage into action potentials.

One particular type of nociceptor is referred to as a silent nociceptor. It can be activated only after inflammation or after tissue damage has occurred. Estimates are that up to 40% of C and 30% of Aδ fibers are silent nociceptors. Following release of chemical injury products,
these previously silent receptors are activated by a wide range of thermal and mechanical stimuli and may also develop a background discharge.

Primary Afferent Fibers
Pain sensation appears to be dependent on stimulating fibers which are specific for signaling real or impending tissue damage (nociceptors). Activation of Aδ nociceptors produces a brief prickling sensation (first pain), while activation of C nociceptors results in a poorly localized burning sensation (second pain) [85]. This has been demonstrated in clinical studies involving recording from individual nerve fibers (microneurography). Only stimulation of fibers connected to nociceptors results in pain [40]. Stimulation of fibers connected to other receptor types at the same or higher frequencies never results in sensations of pain [89]. This modality specificity is referred to as labeled line.

Primary Afferent Fiber Neurotransmitters
Many of the unmyelinated and lightly myelinated fibers contain the excitatory amino acids (EAAs) aspartate and glutamate, as well as a wide variety of neuropeptides including SP, calcitonin gene-related peptide (CGRP), cholecystokinin (CCK) galanin, somatostatin and others. Frequently, these substances are co-localized in the same terminals [4, 31]. Recent evidence points to differential control of these co-localized compounds such that each can be released independently. Administration of noxious, but not innocuous, stimulation results in the selective release of several of these peptides in the spinal dorsal horn [22, 23, 39] as well as in peripheral tissue [98]. In contrast, the EAAs are found in both large- and small-diameter afferent fibers [93, 94] and their release has been demonstrated with low intensity stimuli that activate only Aβ fibers [36], as well as by acute and chronic nociceptive stimuli, including joint inflammation [72, 77].

There are several types of EAA receptor subtypes including N-methyl-D-aspartate (NMDA) and non-NMDA (AMPA/kainate and metabotropic) receptors found postsynaptically on spinal cord dorsal horn cells [9], [69], [92]. Behavioral studies indicate that intrathecal administration of agonists for either NMDA or non-NMDA receptors produces nociceptive behavior [1], [63]. Results from several studies indicate that AMPA/kainate receptors mediate the monosynaptic response from the primary afferent fibers to the dorsal horn neurons and that the NMDA linkage is postsynaptic to interneurons, creating a multisynaptic pathway [14], [72]. Other studies associate AMPA/kainate receptor activation with low threshold fiber stimulation and NMDA receptors with transmission from Aδ and C nociceptive fibers [17].

There is an association of peptides with fiber diameter, i.e. only some C fibers and a small subpopulation of Aδ fibers contain SP. Peptide content of afferent fibers appears to be more closely related to the peripheral target (skin, muscle or viscera) than by the specific modality that activates them [44], [58]. In fact, peptide content of a nerve can change (e.g., the transmitter phenotype of the axon is altered) when the nerve is misattached to an inappropriate peripheral structure [52]. It must be noted that a large proportion of nociceptive dorsal horn cells are contacted by numerous SP-containing synapses [16] and that in animals, blockade of the NK1 receptor which is acted upon by SP reduces post-operative pain [28].

Central Terminal Patterns of Afferent Axons
The dorsal horn of the spinal cord is divided into laminae based on the types of neurons and their organization; these include lamina I (the marginal zone), lamina II (substantia gelatinosa) and laminae III-VI (nucleus proprius). Functionally, lamina X, the area around the central canal, can also be included. The pattern made by the axon terminals is a characteristic of the receptor type. The principle spinal cord target of somatic C nociceptors is ipsilateral lamina II [82], while Aδ nociceptors terminate in ipsilateral lamina I and to a lesser extent lamina V [45]. C nociceptors from the viscera have a more diffuse projection to lamina II which is spread out over several segments as well as bilateral projections to lamina V and X [82]. These projection patterns correspond to the dorsal horn areas with the highest concentrations of cells receiving nociceptive input. The widespread distribution of the visceral C fibers is thought to account for the diffuse quality of visceral pain.

SPINAL COMPONENTS OF NOCICEPTIVE PROCESSING

Nociceptive-Specific Cells

Lamina I and to a lesser degree deeper laminae (particularly V and X) contain many nociceptive-specific (NS) cells that respond selectively to high-threshold, potentially tissue damaging stimuli (Table II). Although some are modality specific, others respond to both thermal and mechanical stimuli applied to their receptive fields as well as to noxious chemical stimuli. Many also fire in response to decreases in pH and during reperfusion after temporary ischemia. Regardless of modality specificity, activity in these cells provides an unambiguous signal that stimulation of nociceptors has occurred. Receptive fields are usually small and may include skin and muscle. Other prominent types of projection neurons in lamina I include (1) thermoreceptors which are activated by cool and inhibited by warming their receptive fields [13] and cells that are excited by noxious cold in addition to heat and pinch [10], [19].

Wide-Dynamic-Range Neurons

Wide-dynamic-range (WDR) neurons are more numerous in the deeper laminae centering around lamina V in the neck of the dorsal horn, although there is a small population found in lamina I [24]. WDR cells take their name from their ability to respond in a graded fashion to both innocuous and noxious stimuli over a wide range of stimulus intensities. They encode stimulus intensity by their firing frequency and respond maximally to very noxious stimuli. In general their receptive fields are larger than those of NS cells and frequently include skin, muscle and viscera. WDR neurons usually receive input, directly and via multisynaptic pathways, from large myelinated (Aβ and Aδ) as well as unmyelinated (C) afferent fibers. This convergence of a full spectrum of inputs onto a single cell is what allows them to have the wide range that gives them their name. Convergence can encompass inputs from afferents encoding innocuous and noxious thermal as well as mechanical inputs. This property enables WDR cells to integrate the net afferent traffic and encode stimulus intensity, irrespective of modality.

Complex Cells

Laminae VI and VII contain a concentration of complex cells; these have large frequently bilateral and/or discontinuous excitatory receptive fields that may cover large portions of the body. In addition, there are other areas of the body where stimulation causes the cells to fire less. These inhibitory receptive fields may be discontinuous with the excitatory ones or
conversely, stimulation with one modality may excite the cell while stimulation at the same site with another type of stimulus (e.g. pinch vs. touch) may inhibit it.

Viscerosomatic Cells

Both WDR and complex cells may receive excitatory input from skin and muscle as well as visceral organs. This convergence is somatotopically organized; this results in a predictable co-projection of specific organs and regions of skin. Thus, some dorsal horn neurons in the left thoracic spinal cord receive input from the coronary vasculature and musculature as well as from the skin of the left shoulder and arm. This convergence provides the anatomical basis for the association of coronary ischemia with painful sensations of the left arm. This convergence can account for most of the visceral referred pain states, in this case, angina (see Fig. 1).

Other Cells

Response properties of cells in the substantia gelatinosa (lamina II, SG) are different than those described previously [8]. They have high levels of ongoing activity and relatively small receptive fields. Most cells in SG are inhibited by high intensity stimulation, the same kind of noxious stimulus that drives NS and WDR cells. Light touch applied to the same receptive field makes these cells fire at higher frequencies. They have been implicated in tonic inhibition of other cells, including those involved in pain transmission [8]. These actions are conceptually, but not anatomically consistent with the original gate control theory of pain transmission [54].

SPINAL MODULATION OF NOCICEPTIVE TRANSMISSION

Clearly, there is a relationship between afferent fiber input and spinal cord output to the brain leading to pain perception. However, even in the processing of acute nociceptive input, this relationship is not immutable, and the output is dependent on far more than mere hard-wiring. Behavioral relevance of the signal, attention, movement and previous experience are all factors. As the pain state progresses toward chronic, the system becomes even more complex. Plasticity of the input-output relationship is the function of several types of modulation; some produce increases in the gain of the system (hyperalgesia) or reduce the threshold (alldynia), while others decrease the output (analgesia).

Spinal Facilitation

One characteristic of some cells with convergent input from A and C fibers (usually WDR cells) is a phenomenon called wind-up. Under normal circumstances, spinal cord cells have a fixed stimulus-dependent response to a defined stimulus. In certain cells, however, if the stimulus (1) activates C fibers and (2) is repeated at frequencies greater than 0.33 Hz, the cellular response increases in both magnitude and duration [55]. Wind-up appears to co-vary with a progressive and sustained partial depolarization of the cell. This brings it closer to threshold and allows smaller afferent inputs to result in action potentials.

Properties of Wind-up

Wind-up appears to be a specific form of spinal sensitization, a more generalized increase in the input-output ratios of nociceptive dorsal horn cells. In addition to the conditioning effect on C-fiber input, spinal sensitization can result in increased receptive field size, such that afferent input from sites that previously did not activate the neuron now evokes a prominent response.
Moreover, low threshold tactile stimulation (via Aβ fibers) also becomes increasingly effective at activating the cell and causing pain behavior. That increased response to low threshold input (alldynia) is due at least in part to spinal rather than peripheral sensitization was demonstrated using electrical stimulation of afferent nerve fascicles [73]. This type of facilitated nociceptive processing is produced following many types of injury including intradermal injection of capsaicin [73], experimental arthritis [20] and several types of localized tissue inflammation [65], including post-operative states [103]. A psychophysical correlate in human volunteers showing enhanced second pain in response to repeated electrical shocks administered faster, but not slower, than 0.3 Hz has been demonstrated [61].

Pharmacology of Wind-up

Both wind-up and most forms of central sensitization are thought to be initiated by the co-release of neurokinins, particularly SP working at NK1 receptors and EAAs, most likely via an NMDA receptor link [26], [18]. Wind-up is blocked by NMDA receptor antagonists [15] and specific antagonists for the NK1 receptor [38]. Interestingly, in the psychophysical studies, the enhanced second pain caused by repeated electrical shocks, but neither first pain nor the baseline levels of the second pain response, was reversed by an NMDA antagonist [61]. Intrathecal NMDA antagonists have been given clinically for severe and intractable neuropathic pain and they reverse the hyperalgesia thought to be due to spinal sensitization [41]. As yet, there is no positive clinical study supporting the use of NK1 antagonists for pain. Endogenous spinal release of prostaglandins and nitric oxide are thought to follow the release of the EAAs and SP [76], [75]; their exogenous administration causes pain behavior, allodynia and hyperalgesia [56]. Conversely, administration of cyclooxygenase inhibitors [49] or nitric oxide synthase inhibitors [53], [62] reduces the development of hyperalgesia and allodynia. Corticosteroids, which block an inducible isozyme of cyclooxygenase, are thought to have antihyperalgesic effects via this mechanism [51]. Other drugs that can suppress the development of spinal wind-up include the opioids, alpha 2-agonists and the N-type calcium channel blockers. The opioids bind to mu receptors in the substantia gelatinosa to block neurotransmitter release from C fibers and to hyperpolarize nociceptive dorsal horn neurons [99]. Alpha 2 receptors are also located in the substantia gelatinosa, presynaptically on C fibers and post-synaptically on dorsal horn neurons. Activation of these receptors depresses C fiber transmitter release [101]. There are an abundance of N-type calcium channels in the dorsal horn. In animal models, acute spinal injection of certain synthetic omega-conopeptides selective for the N-type voltage sensitive channel produces a powerful dose-dependent suppression of both phase 1 (an index of acute pain) and phase 2 (a model for hyperalgesia)[50].

Spinal Inhibition

The activity of dorsal horn nociceptive neurons can be inhibited by a variety of local, intrasegmental and supraspinal mechanisms.

Large Afferent Axon Interactions

Spinal neurons can be inhibited by activation of large-diameter primary afferent fibers or their collaterals. This includes a local spinal circuit initiated by activation of low threshold afferent fibers, which produce primary afferent depolarization [90], a type of presynaptic inhibition of other primary afferents, including C fibers [6], [25]. In the case of primary afferent depolarization, the inhibitory amino acid (IAA), γ-aminobutyric acid (GABA), is thought to
mediate the effect [71]. The process is very specific, and only tissue within the area being stimulated is affected; activation of hair follicle afferents is perhaps the most effective stimulus. Presynaptic inhibition, including that initiated by primary afferent depolarization, reduces the amount of neurotransmitter released from the afferent fibers in response to a fixed afferent input [71]. In psychophysical experiments, vibratory stimuli applied to a painful area to naturally activate large myelinated fibers reduced perception of chronic musculoskeletal pain [48]. It has been proposed that the pain reduction following dorsal column stimulation takes advantage of this primary afferent depolarization by electrically activating collaterals of primary afferent fibers, which synapse in the dorsal horn near their spinal cord entry level. Electrical stimulation of the dorsal surface of the spinal cord with parameters similar to those used in the clinic causes a massive spinal release of GABA [46].

Receptors for inhibitory neurotransmitters other than GABA are also located on primary afferent fibers and appear to be involved in presynaptic inhibition resulting from other mechanisms; these include opiate receptors (μ and δ with a higher percentage of μ) and glycnergic, α2-adrenergic, serotonergic and cholinergic receptors. Most of these receptor types are also located post-synaptically on the nociceptive dorsal horn cells. Blockade of either GABA or glycine receptors results in increases in background firing and greatly enhanced responses evoked by low threshold stimulation [79], [80]; this indicates that they participate in a tonic inhibition. Loss of IAA containing interneurons could result in a severe allodynia.

Small Afferent Axon Interactions

Stimulation of nociceptive afferent fibers can also lead to inhibition of dorsal horn cells; these processes involve both spinal and supraspinal elements. Inhibition of nociceptive evoked activity in a subpopulation of WDR spinothalamic tract cells is elicited by high intensity, but not low intensity stimulation of much of the body, including the side contralateral to the cell and its excitatory receptive field [27]. Severing the cervical spinal cord only minimally diminished the effect, indicating that the mechanism occurs primarily within the spinal cord. Viscerosomatic neurons typically are inhibited from sites distant from their excitatory receptive fields via similar heterosegmental circuits [57]. In both cases, magnitude of the inhibition is directly related to the strength of the inhibitory stimulus, and WDR neurons are under inhibitory propriospinal control to a greater extent than NS neurons. In one study, 92% of WDR vs. 10% of NS cells had distant inhibitory receptive fields [57].

Supraspinal Modulation

Descending modulation can be tonic or phasic, inhibitory or excitatory and results from activity originating in the spinal cord (spinobulbospinal pathways) or from supraspinal origin. It can be mediated via presynaptic (on primary afferent fibers) or postsynaptic actions. A powerful steady-state bulbospinal inhibitory system limiting the expression of C fiber input has been postulated [29], [91]: it can change WDR cells into cells that respond selectively to low threshold input [91]. Activation of midbrain (periaqueductal gray) or brain stem sites (raphe nuclei) thought to be involved in the “endogenous analgesia system” results in a similar phenomenon. WDR cells no longer respond to noxious stimulation of their receptive fields but are still activated by low threshold input. Stimulation of sensorimotor cortex or within the pyramidal tracts can produce the opposite effect; responses to low threshold input are suppressed and those to nociceptive stimulation are unaltered [60].
Activation of nociceptive afferents appears to turn on descending inhibitory systems through a spinobulbospinal pathway. These systems do not exhibit somatotopy; that is, noxious stimulation on one body part activates descending inhibition that influences the whole body. This is the basis of the descending noxious inhibitory control system (DNIC [42, 43]) or counterirritation theories. Using modulation of the polysynaptic flexor response, Willer and colleagues [95] have demonstrated that DNIC is operative in normal human subjects. In animal studies, following noxious, but not innocuous peripheral stimulation, there is an increase in spinal release of several neurotransmitters including enkephalin [100], serotonin (5-hydroxytryptamine [5-HT]) [77], and norepinephrine (NE) [88] as well as IAAAs. Serotonin release in the lumbar spinal cord has been demonstrated following stimulation of a branch of the trigeminal nerve illustrating the lack of somatotopy [88]. As the strength of the afferent input increases, strength of the descending inhibitory forces seems to increase in parallel. Such growing descending inhibition has been observed during the development of experimental arthritis [70].

The presumed source of both monoamines are various brainstem nuclei: the raphe nuclei for 5-HT and the more lateral locus coeruleus-subcoeruleus complex, lateral reticular nucleus and magnocellular region of the reticular formation for NE. Direct stimulation of the nucleus raphe magnus evokes the spinal release of 5-HT as well as glycine [78], and raises the threshold of escape reflexes [59]. Similarly, stimulation of the relevant brain stem nuclei elicits spinal release of NE [2], [30] and raises withdrawal thresholds [35]. Both monoamines are thought to work through pre- and postsynaptic mechanisms. The majority of the inhibitory 5HT receptor subtypes (they are numerous) are negatively coupled to adenylate cyclase via regulatory G-proteins which frequently act via opening potassium channels and causing a subsequent hyperpolarization [3]. The exception is the 5-HT3 subtype which directly opens up a selective cation channel [97].

There appears to be an opioid link in spinal 5-HT analgesic actions because pretreatment with naloxone inhibits intrathecal 5-HT-induced-antinociception. Conversely, pretreatment with 5-HT antagonists reduces the efficacy of intrathecal morphine [37]. This interactive pattern appears to be duplicated in nucleus raphe magnus [47] in which antinociception is caused by microinjection of morphine and is reduced by coinjection of 5-HT antagonists. The relationship between NE and morphine appears to be one way rather than reciprocal. Thus, naloxone pretreatment has no effect on NE antinociception [64], but a2-antagonists, NE-depleting agents including reserpine, and lesions within the noradrenergic system all interfere with morphine analgesia [5], [12], [68].

Analgesic actions of 5-HT, NE and their agonists are potentiated by prior administration of monoamine oxidase (MAO) inhibitors and monoamine reuptake inhibitors. These drugs lead to increased extracellular levels of 5-HT and NE in the spinal cord and increased pain thresholds [102]. Tricyclic antidepressants relieve pain in addition to their effects on mood: this may be a function of their action as monoamine reuptake blockers [84]. Selective 5-HT reuptake inhibitors have also been used to treat chronic pain [74]. Local anesthetics of the ester class, such as tetracaine, are MAO inhibitors and also block NE reuptake [67]. Thus, they increase available monoamines by two mechanisms. MAO inhibitors and reuptake inhibitors both potentiate the actions of morphine (see Table III) [84].
Basal responses to transient nociceptive stimuli and acute morphine analgesia are unaffected by NMDA receptor antagonists; however, development of morphine tolerance is prevented at the spinal level by pretreatment with non-competitive NMDA receptor antagonists, including some that are presently in clinical use such as ketamine [87]. Once opiate tolerance is expressed, it is not reversed by administration of these agents. Interestingly, naloxone precipitated opiate withdrawal results in a massive spinal release of EAAs, including glutamate [34]. Interactions between morphine analgesia, morphine tolerance, and the primary afferent peptide CCK are more complex. CCK diminishes the analgesic effects of morphine. Antagonists to the CCK-B receptor subtype enhance acute morphine analgesia indicative of a tonic CCK modulation [21], [81]. Natural decreases in CCK expression during peripheral inflammation may be responsible for the reported increased analgesic potency of morphine in these states. Chronic coadministration of CCK-B receptor antagonists with morphine (systemically or intrathecally) also prevents the development of morphine tolerance [21], and there are indications that administration of CCK-B antagonists after development of tolerance causes reversal [96], [33]. CCK-B and NMDA receptors are now postulated to mediate opiate tolerance via a convergent second-messenger pathway. It is hoped that these studies will soon open up clinically relevant opportunities to bypass development of morphine tolerance.

SUMMARY

The systems activated by tissue-injuring stimuli are complex. The nociceptive primary afferents have little spontaneous activity under normal conditions, however, after tissue injury they display long lasting ongoing activity. This results, in part, because the injury elicits the release of active factors that sensitize and/or excite the peripheral nerve terminal. If threshold is lowered to the extent that body temperature and the pressure of edema are adequate stimuli this results in spontaneous pain. This phenomenon is mediated by a variety of blood borne active factors released during plasma extravasation, by agents released from local inflammatory cells and by neurotransmitters released from the peripheral terminals of the primary afferent fibers themselves. Well-defined projections into the dorsal horn convey the “pain message” to at least two well-defined populations of neurons; those that are nociceptive specific and those that display an intensity-linked discharge over a range of stimuli from innocuous to noxious. Convergence from various fiber types, modalities and end organs permits the encoding of afferent traffic with respect to intensity and location. The convergence of axons from somatic and visceral structures reflects the mechanism for the so-called referred pain state. Most importantly, these dorsal horn systems have a dynamic component in addition to the hard wiring; their output can be regulated both up and down. The up-regulation provides the basis for much of the facilitated processing that is believed to account for a significant percentage of the post-injury pain state. The facilitated state has a unique pharmacology with the underlying mechanisms reflecting a cascade of actions that start with the NMDA receptor and proceed through the spinal release of intermediaries such as prostaglandins and nitric oxide. Conversely, the ability to down-regulate the dorsal horn stimulus response function accounts for the powerful control exerted by a wide variety of diverse factors, including the spinal delivery of opioid and nonopioid analgesics and the “endogenous analgesia system”.

These linkages reflect the complexity of the encoding mechanisms that transduce the tissue injury into the behavioral sequelae known as pain. This article also tries to emphasize that although considerable progress has been made in the past decade, the current pace of research promises greater insights.
REFERENCES


18. Dickenson AH, Sullivan AF: Evidence for a role of the NMDA receptor in the frequency dependent potentiation of deep rat dorsal horn nociceptive neurones following C fibre stimulation, Neuropharmacol. 26:1235-8, 1987


41 Kristensen JD, Svensson B, Gordh T Jr: The NMDA-receptor antagonist CPP abolishes neurogenic 'wind-up pain' after intrathecal administration in humans. Pain, 51:249-253, 1992
45 Light AR, Perl ER: Spinal termination of functionally identified primary afferent neurons with slowly conducting myelinated fibers. J Comp Neurol, 186:133-150, 1979
50 Malmberg AB, Yaksh TL: Effect of continuous intrathecal infusion of omega-conopeptides, N-type calcium-channel blockers, on behavior and antinociception in the formalin and hot-plate tests in rats. Pain, 60:83-90, 1995
52 McMahon SB, Gibson S: Peptide expression is altered when afferent nerves reinnervate inappropriate tissue. Neurosci Letts, 73:9-15, 1987
<table>
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<tr>
<th></th>
<th>Reference</th>
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<tr>
<td>55</td>
<td>Mendell LM: Physiologic properties of unmyelinated fiber projections to the spinal cord. Exp Neurol, 16:316-332, 1966</td>
</tr>
<tr>
<td>72</td>
<td>Schouenborg J, Sjölund BH: First-order nociceptive synapses in rat dorsal horn are blocked by an amino acid antagonist. Brain Res, 379:394-8, 1986</td>
</tr>
</tbody>
</table>


Sorkin LS: NMDA evokes an L-NAME sensitive spinal release of glutamate and citrulline. Neuroreport, 4:479-482, 1993

Sorkin LS, McAdoo DJ: Amino acids and serotonin are released into the lumbar spinal cord of the cat following intradermal capsaicin injections. Brain Res, 607:89, 1993

Sorkin LS, McAdoo DJ, Willis WD: Raphe magnus stimulation-induced antinociception in the cat is associated with release of amino acids as well as serotonin in the lumbar dorsal horn: Brain Res, 618:95-108, 1993


Stanfa LC, Dickenson AH: Cholecystokinin as a factor in the enhanced potency of spinal morphine following carrageenin inflammation. Brit J Pharmac, 108:967-973, 1993


Szolcsányi J: Antidromic vasodilatation and neurogenic inflammation. Agents and Actions, 23:4-11, 1988


Wall PD: Excitability changes in afferent fibre terminationsand their relation to slow potentials. J Physiol, 142:1, 1958


TABLE I

NEUROACTIVE SUBSTANCES INVOLVED
IN PERIPHERAL SENSITIZATION

<table>
<thead>
<tr>
<th>Substance</th>
<th>Source</th>
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<tr>
<td>Substance P</td>
<td>Nerve terminals</td>
</tr>
<tr>
<td>Glutamate</td>
<td>Nerve terminals</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>Plasma kininogen</td>
</tr>
<tr>
<td>Histamine</td>
<td>Platelets, mast cells</td>
</tr>
<tr>
<td>Protons (low pH)</td>
<td>Ischemia, damaged cells</td>
</tr>
<tr>
<td>Prostaglandins</td>
<td>Arachidonic acid-damaged cells</td>
</tr>
<tr>
<td>Interleukins</td>
<td>Mast cells</td>
</tr>
<tr>
<td>Tumor necrosis factor (TNF-α)</td>
<td>Mast cells</td>
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### TABLE II

**CHARACTERISTICS OF DIFFERENT DORSAL HORN NOCICEPTIVE NEURONS**

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Laminar Location (Predominant)</th>
<th>Light Touch</th>
<th>Pinch or Squeeze</th>
<th>Receptive Field Size</th>
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<tbody>
<tr>
<td>NS</td>
<td>Lamina I</td>
<td>No Res</td>
<td>+++</td>
<td>Small</td>
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<tr>
<td>WDR</td>
<td>Lamina V</td>
<td>+</td>
<td>+++</td>
<td>Medium</td>
</tr>
<tr>
<td>Complex</td>
<td>Lamina VI-VIII</td>
<td>+++</td>
<td>+++ and -</td>
<td>Large</td>
</tr>
<tr>
<td>Substantia</td>
<td>Lamina II</td>
<td>-- or ++</td>
<td>-- or ++</td>
<td>Small</td>
</tr>
<tr>
<td>gelatinosa</td>
<td></td>
<td></td>
<td></td>
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### TABLE III

**INTERACTIONS OF OPIATES WITH NEUROTRANSMITTER SYSTEMS**

<table>
<thead>
<tr>
<th>Substance</th>
<th>Increased or Decreased Morphine Effect</th>
<th>Blocks or Reverses Tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT agonists</td>
<td>Increased</td>
<td>__</td>
</tr>
<tr>
<td>α2-adrenergic</td>
<td>Increased</td>
<td>__</td>
</tr>
<tr>
<td>agonists</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCK-B</td>
<td>Decreased</td>
<td>Blocks and Reverses</td>
</tr>
<tr>
<td>NMDA antagonists</td>
<td>No Effect</td>
<td>Blocks</td>
</tr>
</tbody>
</table>
FIGURE LEGEND

Figure 1 Visceral afferent nociceptive fibers and cutaneous afferents synapse on common dorsal horn cells. Activity in the visceral structure is interpreted as coming from the somatic one. Afferent visceral input from a particular structure is projected onto the linked cutaneous structure in a characteristic pattern. In this example, afferents from the medial forearm converge with visceral afferents from myocardium. Ischemic activation of the visceral afferent is perceived as angina pain coming from the medial forearm.
New Antiepileptic Drugs in the Treatment of Neuropathic Pain: A Review

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New Antiepileptic Drugs in the Treatment of Neuropathic Pain: A Review

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Abstract

Neuropathic pain (NeP) is a complex chronic condition with highly variable clinical presentations and responses to treatment. NeP can result from injury, systemic disease, or infection. These may trigger neuroplastic changes in primary afferent axons and dorsal root ganglia and remodeling in the spinal dorsal horn. Hyperexcitability of pain afferents, crosstalk between pain afferents and sympathetic fibers, and an increase in ascending pain signals contribute to the development and maintenance of NeP. Research has uncovered many of the biochemical interactions that might be involved in NeP, including changes in ion channel expression and central and peripheral neuropeptides. Many drugs have been employed to treat NeP, but newer antiepileptic drugs may be particularly useful. These drugs modulate ion channel function and may also modify the actions of neurotransmitters involved in pain processing. Recent results from controlled clinical trials have suggested considerable promise for several of these agents in patients with NeP.

Key Words

Antiepileptic drugs, chronic, diabetes, ion channel, pain, peptide

Neuropathic pain (NeP) is chronic pain initiated by nervous system lesions or dysfunction and maintained by a number of mechanisms. Excess stimulation of nociceptive pathways or damage to non-nociceptive pathways alters the balance between painful and nonpainful inputs so that pain results without nociceptor stimulation. Examples of NeP include trigeminal neuralgia, postherpetic neuralgia, peripheral NeP associated with diabetes mellitus or HIV infection, cancer pain, central post-stroke pain, low back and other post-traumatic pain, and complex regional pain syndrome.
Neuropathic pain is described by a variety of terms such as burning, shooting, or lancinating and may be present without demonstrable physical findings. NeP sensations are diverse, but three symptoms—numbness, tingling, and increased pain due to touch—appear to predominate. These symptoms illustrate the negative (sensory deficit) as well as positive (paresthesia and allodynia/hyperalgesia) phenomena that distinguish neuropathic from nociceptive pain. NeP is very difficult to treat. Its resistance to opioids has been reported, although more recent studies have shown that opioids at higher doses are effective in treating NeP. Other pharmacotherapies that have been employed with variable efficacy in patients with NeP include topical lidocaine, tricyclic antidepressants, local anesthetics, and N-methyl-D-aspartate (NMDA) receptor antagonists. Sites of action for some of the different drugs used to treat NeP are summarized in Figure 1.

Antiepileptic drugs (AEDs) are an attractive alternative for the treatment of NeP. Although their precise mechanisms vary, AEDs generally enhance inhibitory neurotransmission, reduce excitatory neurotransmission, and regulate cation channel conductance. There is also some evidence that AEDs have neuroprotective effects; however, an effect of early use of AEDs in preventing NeP has yet to be demonstrated.

Pathophysiology of NeP

Several cellular and molecular mechanisms operating over different periods of time are thought to be involved in the abnormal peripheral and central nervous system activity associated with NeP (Figure 2). The mechanisms are complex, and the development and persistence of neuropathic pain after nerve injury may be associated with abnormalities that arise in uninjured as well as injured nerves. Table 1 summarizes the pathophysiologic mechanisms and related symptoms and therapeutic targets.

Ion Channels

Neuropathic pain often arises after peripheral nerve injury and the formation of neuromas, which can generate spontaneous ectopic discharges or become hypersensitive to mechanical or chemical stimulation. Hyperexcitability of neuromas has been associated with the ectopic accumulation of voltage-gated sodium channels in axon membranes of injured nerves. Calcium channel expression may also increase in injured primary afferent neurons.

Cytokines

Receptors for inflammatory cytokines such as tumor necrosis factor α (TNF-α) can also accumulate in injured sensory neurons and alter their function. Proinflammatory cytokines are involved in a wide and diverse range of NeP conditions associated with both traumatic and infectious processes. Interleukins 1β and 6 and TNF-α are elevated in vasculitic neuropathy, chronic inflammatory demyelinating neuropathy, and noninflammatory chronic neuropathy. Cytokine levels are correlated with the degree of axonal degeneration, the presence of endoneurial macrophages or epineurial T cells, and NeP. Cytokine levels also rise after nerve transection, and this elevation is correlated with allodynic behavior that may be linked to glutamate release and NMDA receptor activation. Microglia also are activated in the spinal cord in several rat models of mononeuropathy and produce a variety of cytotoxic molecules including proinflammatory cytokines. Raghavendra et al reported that daily administration of...
minocycline, an inhibitor of microglial activation, attenuated the development of mechanical allodynia and hyperalgesia in rats when initiated 1 hour before L5 spinal nerve transection but did not attenuate established allodynia and hyperalgesia when initiated 5 days after transection. Similar findings in a rat model of sciatic nerve inflammation were reported by Ledeboer et al.29 Little studied as yet in relation to NeP is phenotypic shift of immune cells from β2- to α1-adrenergic receptor expression, which reverses the β2-receptor–mediated inhibition of proinflammatory cytokine production. This shift occurs in some chronic inflammatory conditions, such as polyarticular juvenile rheumatoid arthritis,30 and could be a factor in some persistent NeP states, such as complex regional pain syndrome.25

**Demyelination**

Demyelination of peripheral or central axons is also often associated with NeP. Pain, including trigeminal neuralgia, is a frequent symptom of multiple sclerosis,31 and mice deficient in periaxin, a protein thought to be involved in myelin stabilization, exhibit peripheral demyelination accompanied by severe mechanical allodynia and thermal hyperalgesia.32

**Sympathetic Sprouting**

Neurons in dorsal root ganglia (DRGs) can receive axon sprouts from postganglionic sympathetic fibers as well as ephaptic connections from neighboring cells. These anatomic changes are associated with functional hyperexcitability after peripheral nerve transection.33 The role of sympathetic nervous system sprouting is supported by the observation that sympathectomy virtually abolished mechanical allodynia and ongoing pain behaviors and reduced cold-elicited allodynia in a nerve-ligation model of NeP.34

**Neurotrophins**

Neurotrophins have been implicated in the induction of sympathetic sprouting and development of NeP after peripheral nerve injury. In rats that had undergone L5 spinal nerve transection, the administration of antisera to nerve growth factor (NGF), neurotrophin-3, and brain-derived neurotrophic factor reduced sympathetic sprouting and attenuated the lesion-induced increase in foot-withdrawal responses to von Frey hair stimuli.35 In humans, decreased levels of NGF in the affected skin have been implicated in the causation of cutaneous hypoalgesia in leprous neuropathy, while patients with traumatic neuropathy and chronic skin hyperalgesia and allodynia show marked local increases of NGF levels.36

**Enzymes**

Membrane-type 5 matrix metalloproteinase (MT5-MMP) has been implicated in injury-associated spinal cord remodeling and development of NeP. Sciatic nerve damage results in sprouting of Aβ afferents from laminae III–VI and into lamina I of the dorsal horn and in the development of mechanical allodynia. Neither sprouting nor allodynia occurs after nerve damage in mice lacking the gene for MT5-MMP.37

**Neuropeptides**

Nerve injuries associated with the development of NeP alter the expression of neuropeptides and their receptors. Vanilloid receptor 1 (VR1) is expressed on peripheral terminals of Aδ and C fibers. However, in rats with streptozotocin-induced diabetes, peripheral terminals of Aβ fibers also express VR1.38 Substance P (SP) is normally released from the central terminals of Aδ and
C fibers to bind with neurokinin-1 (NK-1) receptors on nociceptive neurons in the dorsal horn.\textsuperscript{39} NK-1 mRNA expression in the mouse lumbar dorsal horn is increased after partial sciatic nerve ligation, and this rise is correlated with thermal hyperalgesia.\textsuperscript{39} These results have prompted the suggestion that nerve injury results in synthesis and tonic release of SP by Aβ fibers, which initiates ongoing excitation of NK-1–expressing spinal nociceptive neurons.\textsuperscript{40}

**Centralization**

The enduring quality of NeP may result, at least in part, from a “centralization” in which abnormal peripheral activity fosters increased dorsal horn excitability. While peripheral hyperexcitability is mediated in part by ion channel plasticity, central hyperexcitability is partly a result of abnormal primary afferent release of neuropeptides.\textsuperscript{41} Action potential “wind-up” may result from NMDA potentiation, the cumulative effect of SP-mediated slow excitatory potentials, or calcium channel facilitation by metabotropic glutamate receptors.\textsuperscript{42}

**Aβ Sprouting**

Crosstalk between Aβ and Aδ or C fiber pathways can develop in the dorsal spinal cord after peripheral nerve injury or chronic inflammation (Figure 3).\textsuperscript{43} Normally, low-threshold Aβ primary axons terminate in dorsal horn laminae III–IV. After peripheral nerve damage or inflammation, Aβ fibers may project collaterals into laminae I–II, where they form synapses onto secondary neurons associated with pain pathways.\textsuperscript{44,45} The actions of these ectopic terminals are not fully understood and may be affected by both time and stimulus intensity,\textsuperscript{39} but they are thought to contribute to the development of mechanical allodynia.\textsuperscript{21}

**Sympathetic-Somatosensory Crosstalk**

As noted above, crosstalk between sympathetic and somatosensory afferents can develop in neuromas and DRGs. Sympathetic axons are present in neuromas,\textsuperscript{47} and α-adrenoceptor–mediated excitatory coupling has been demonstrated in both neuromas and DRGs.\textsuperscript{33,48} Results from studies that combined immunocytochemical and behavioral methods indicated that the sympathetic-sensory coupling in the DRG correlates with the type of injury but not necessarily with the types of pain behavior displayed by experimental animals.\textsuperscript{49,50}

**GABA Down-regulation**

Spinal inhibitory interneurons modulate the peripheral-to-central transmission of pain signals, thus “gating” ascending sensory information.\textsuperscript{51} γ-Aminobutyric acid (GABA) and glycine and their receptors are abundant in the superficial dorsal horn,\textsuperscript{52,53} but their levels are regulated by primary afferent input and change significantly after nerve injury. Sciatic nerve transection decreases the number of GABA-immunoreactive cells in dorsal horn laminae I–III,\textsuperscript{52} and this may “open the gate” to allow more excitatory signals from pain (or nonpain) pathways to reach the brain. Nerve damage also reduces expression of GABA\textsubscript{A} receptor α2 subunit mRNA in DRG cells, and this may disrupt the normal presynaptic inhibition that modulates neurotransmitter release by these cells.\textsuperscript{54} In one autoradiographic experiment, presynaptic GABA\textsubscript{B} receptors in the dorsal horn were down-regulated after sciatic nerve transection. Surprisingly, this study also showed up-regulation of GABA\textsubscript{A} receptors in the same region.\textsuperscript{55}

The importance of alterations in GABAergic neurotransmission in NeP is supported by observations that a decrease in allodynia following electrical spinal cord stimulation is associated
with increased spinal GABA concentration and that intrathecal GABA administration can reverse thermal and mechanical hyperalgesia resulting from chronic nerve constriction. However, some investigators have questioned the importance of changes in the GABAergic system for the development of NeP. Polgár and associates reported that thermal hyperalgesia following chronic constriction injury was not related to any change in number of dorsal horn neurons positive for GABA or glycine.

**Glutamatergic Neurotransmission**

Increased glutamatergic neurotransmission may also contribute to hyperexcitability and NeP. Repeated noxious stimulation leads to temporal summation of dorsal horn excitatory postsynaptic depolarizations, and this amplification is reduced by the NMDA receptor antagonist d-2-amino-5-phosphonovaleric acid (d-APV), suggesting mediation by an increase in glutamate release from primary afferents and subsequent binding to NMDA receptors. Intrathecal NMDA causes an increase in spontaneous activity of dorsal horn neurons that can be reversed by d-APV. Persistent inflammation that gives rise to hyperalgesia is also associated with up-regulation of metabotropic glutamate receptors in the dorsal horn.

Dorsal horn neurons express α-amino-3-hydroxy-5-methylisoxazol propionic acid (AMPA)/kainate-type glutamate receptors; these non-NMDA receptors are thought to be primarily involved in detecting and responding to innocuous stimuli, but AMPA/kainate-NMDA receptor interactions are involved in C-fiber wind-up and long-term potentiation in dorsal horn neurons. In rat neocortical slices, potentiation of AMPA currents is a necessary precedent for potentiation of NMDA currents.

Glutamatergic transmission is potentiated by neuropeptides. For example, thyrotropin-releasing hormone has a slow priming effect that enhances NMDA receptor–mediated nociceptive transmission in the dorsal horn. Peripheral interactions between NK1 and NMDA receptors may also potentiate pain. NK1 receptor activation is thought to potentiate glutamatergic transmission in the spinal cord via NMDA-independent mechanisms.

Protein kinase C (PKC) potentiates NMDA currents by reducing the magnesium block and increasing the probability of channel openings. An additional consequence of protein phosphorylation is tolerance to opioids, which may result from desensitization of the opioid receptor by G-protein kinase 3.

Glutamatergic neurotransmission, most notably that involving NMDA receptors, also results in significant damage-associated changes in the anatomy of the spinal cord. For example, sciatic nerve transection results in degeneration of spinal dorsal horn neurons, and this apoptosis can be prevented when the NMDA antagonist MK-801 is injected before transection and then continuously infused. Nociceptive processing also involves the expression of immediate early genes, a process partially regulated by glutamate receptors. Activity-dependent stimulation of kinases such as extracellular signal-regulated protein kinase, the Ras cascade, and other transcriptional factors appears to be involved in inflammatory pain and NeP.
AED Mechanisms of Action

The mechanisms of action of AEDs are considered in detail in a number of recent reviews. These mechanisms are considered briefly in this section and are summarized in Table 2 before discussion of their correlations with NeP relief.

Gabapentin/pregabalin
Gabapentin and pregabalin bind to the α₂δ subunit of VDCCs. The α₂δ subunit may be common to all VDCCs, suggesting that gabapentin could modulate the activity of more than one type of channel. Both gabapentin and pregabalin bind to α₂δ subunits on presynaptic P/Q-type calcium channels and inhibit the potassium-evoked release of norepinephrine. Gabapentin also blocks PKC-induced glutamate release from perfused slices of the rat caudal trigeminal nucleus. This is notable because substance P activates PKC.

Analgesia achieved with gabapentin and pregabalin may be genotype-dependent, as 11 inbred mouse strains showed significantly different analgesic sensitivities to these drugs. Gabapentin may also have significant effects on GABAergic neurotransmission. Administration of gabapentin to patients with epilepsy elevated brain GABA levels to a greater degree than treatment with other AEDs.

Lamotrigine
Lamotrigine stabilizes neuronal membranes and inhibits the evoked release of glutamate in vitro. It binds to the α subunit of voltage-dependent sodium channels (VDSCs), and it also inhibits R-type calcium currents. In one animal study, the ability of lamotrigine to inhibit veratridine-induced neurotransmitter release at therapeutic concentrations was attributed to its VDSC-blocking properties.

Oxcarbazepine
Oxcarbazepine inhibited high-frequency repetitive firing of sodium-dependent action potentials in cultured neurons and reduced L-type calcium currents in DRG neurons by approximately 30%. It may inhibit neuronal activity by blocking sodium influx.

Topiramate
Topiramate acts as a GABA receptor agonist, an AMPA/kainate receptor antagonist, a carbonic anhydrase inhibitor, and a sodium and calcium channel modulator. It has been shown to increase GABA-mediated chloride currents and to reduce tetrodotoxin-sensitive sodium currents in a dose-dependent manner. Topiramate has also been shown to inhibit AMPA/kainate-elicited calcium influx by up to 60%. Results from a transcranial magnetic stimulation study showed that topiramate significantly decreased intracortical excitability.

Zonisamide
Zonisamide modulates ion channels, acts as a serotonin/dopamine agonist, and inhibits nitric oxide synthetase. It also scavenges free radicals. Zonisamide has been shown to block sustained action potential firing in spinal neurons and to reduce T-type, but not L-type, calcium currents in cultured rat cortical neurons. Zonisamide also increases dopamine concentrations and has a biphasic effect on serotonin levels (effective concentrations enhanced, while supraeffective concentrations reduced, serotonergic neurotransmission).
Levetiracetam
Levetiracetam irreversibly inhibits voltage-dependent calcium currents in N-type (but not in L-, P-, or Q-type) channels, which reduces repetitive action potential generation, and decreases the voltage-gated potassium current. The reduction in action potential with levetiracetam has been attributed to moderate inhibition of the delayed rectifier potassium current.

Felbamate
Felbamate inhibits NMDA-evoked responses but enhances GABA-evoked responses in cultured hippocampal neurons. This effect probably results from felbamate’s interaction with the channel-blocking site (but not the glycine-binding site) of the NMDA receptor. A specific action of felbamate at the channel-blocking site is supported by the fact that its ability to decrease evoked neuronal activity depends on the absence of extracellular magnesium.

Tiagabine
Tiagabine is a nipecotic acid derivative that binds to the GABA reuptake transporter GAT-1 and inhibits presynaptic reuptake of extracellular GABA by neurons and glia. Tiagabine also potentiates GABA<sub>A</sub> receptor currents, which activate GABA<sub>B</sub> receptors, an effect associated with antinociception in rats with peripheral neuropathy due to chronic nerve constriction.

Mechanisms of Analgesia With the AEDs
As the preceding review of the individual drugs indicates, the newer AEDs have several distinct mechanisms of action that may make them useful in the treatment of NeP. These mechanisms include calcium channel blockade (gabapentin, pregabalin, oxcarbazepine, and levetiracetam); NMDA antagonism (gabapentin, lamotrigine, and felbamate); sodium channel blockade (lamotrigine, oxcarbazepine, and topiramate); GABA agonism (gabapentin, pregabalin, topiramate, felbamate, and tiagabine); serotoninergic and dopaminergic activity (zonisamide); and nitric oxide antagonism (zonisamide).

Calcium Channel Blockade
Spontaneous or evoked pain is mediated in part by activation of voltage-sensitive calcium channels, which are abundant in the peripheral and central nervous systems. There are six types of calcium channel (namely, L, N, P/Q, R, and T), expressed throughout the nervous system. The L-, N-, and P/Q-type calcium channels have been shown to be involved in nociception. Blockers of N-type calcium channels have proved effective in a variety of animal models of NeP.

NMDA Receptor Antagonism
The NMDA ionophore is located on postsynaptic neurons in the dorsal horn. Peripheral nerve injury results in significant increases in glutamate at this site, which opens the NMDA channel, causing an influx of calcium, which in turn initiates a signaling cascade that results in spinal “wind-up.” The exact role of the AMPA/kainate receptors is not fully understood, but it is believed that activation of this receptor by glutamate induces a short excitatory postsynaptic potential that removes the magnesium block of the NMDA channel. This results in a priming effect of the NMDA channel leading to a prolonged depolarization response.
NMDA antagonists have been shown to significantly reduce correlates of NeP in various animal models: thermal hyperalgesia in the sciatic nerve ligation model\textsuperscript{117-119} and tactile alldynia in the spinal nerve ligation,\textsuperscript{120} intrathecal strychnine,\textsuperscript{121} streptozotocin-induced diabetes,\textsuperscript{122} and spinal ischemia\textsuperscript{123} models. These studies demonstrate that all components of the allodynic and hyperalgesic state produced by a wide range of nervous system lesions are sensitive to competitive and noncompetitive antagonists of the NMDA receptor ionophore.

The evidence from human studies is minimal. A few studies have demonstrated efficacy of NMDA antagonists such as ketamine in NeP, but only with accompanying side effects.\textsuperscript{124,125} However, several double-blind placebo-controlled studies have demonstrated efficacy for NeP of ketamine and other NMDA antagonists at tolerable doses.\textsuperscript{15,126}

**Sodium Channel Blockade**

Several lines of evidence suggest that both spontaneous and evoked pain after nervous system injury is mediated in part by increased density and altered distribution of voltage-sensitive sodium channels in injured axons and associated DRGs.\textsuperscript{21,127,128} Sodium channel antagonists reduce spontaneous and evoked pain in animal models of NeP.\textsuperscript{13,129} Importantly, these antagonists do not block normal afferent condition.\textsuperscript{130}

**GABA Agonism**

GABA is widely distributed throughout the brain and spinal cord. Activation of the GABA\textsubscript{A} receptor results in an increase in chloride conductance and hyperpolarization of the neuron.\textsuperscript{131} Animal studies have shown that the administration of GABA\textsubscript{A} agonists into the spinal cord leads to antinociception, whereas their supraspinal administration leads to hyperalgesia. The GABA\textsubscript{B} receptor is G-protein–coupled. Its activation evokes a hyperpolarization of the membrane mediated by an increase in potassium conductance or a decrease in opening of voltage-sensitive calcium channels that serve to attenuate terminal transmitter release.\textsuperscript{132,133} These receptors are located at spinal and supraspinal sites, both of which seem to play a role in antinociception, although the spinal site appears to play a dominant role.\textsuperscript{134} There is substantive evidence from animal studies demonstrating the analgesic effect of intrathecally delivered GABA\textsubscript{B} agonists in a variety of pain models.\textsuperscript{135,136} In contrast, human studies have not been as consistent in either nociceptive or NeP syndromes.\textsuperscript{137}

**Serotonin/Dopamine System**

The exact role of the serotonergic and dopaminergic systems in antinociception is unclear. There are serotonin receptors throughout the nervous system. Peripherally, serotonin activates nociceptors and enhances their response to bradykinin.\textsuperscript{138} In the spinal cord and supraspinal regions, multiple serotonin receptor subtypes, along with dopamine receptors, may play a role in nociception. However, agonism and antagonism of these receptors have yielded many conflicting results, and the role of these receptors in analgesia is poorly understood.\textsuperscript{139,140}

**Nitric Oxide Antagonism**

Nitric oxide (NO) is located at spinal and supraspinal levels and acts as an intercellular messenger and neuromodulator.\textsuperscript{141} It is thought that NO plays a role in nociceptive processing and induction of hyperalgesia in the spinal cord.\textsuperscript{142,143} The role of NO in supraspinal nociception is unclear.
Clinical Efficacy of the Newer AEDs in the Treatment of NeP

Among the older or established AEDs, carbamazepine has FDA approval in the United States for the treatment of trigeminal neuralgia. In a recent small randomized, placebo-controlled trial, sodium valproate provided significant subjective improvement of painful diabetic neuropathy and was well tolerated, with only 1 withdrawal from treatment, which was due to elevated aminotransferase levels.

Ten AEDs that have been introduced since the early 1990s, of which 9 are approved in the United States, are often referred to collectively as the new or newer AEDs. Several of the newer AEDs have been evaluated in patients with NeP. Results from the most important of these studies are summarized below and in Table 3.

Although the clinical trial results are promising overall, several limitations of the evidence concerning AEDs for NeP are noteworthy. First, most of the large randomized controlled trials have examined only two pain syndromes, peripheral diabetic neuropathy and postherpetic neuralgia. The applicability of these trials to other NeP syndromes has yet to be determined. Second, many of the studies are underpowered, and although the results are statistically significant, their clinical significance is unknown. Third, studies of some agents have yielded conflicting results that make it difficult difficult to determine clinical significance (eg, topiramate). Fourth, AEDs have many dose-limiting side effects that may preclude dose increases into the therapeutic range for NeP.

Gabapentin

Gabapentin has been studied extensively in patients with NeP. Several small-scale trials found gabapentin effective for NeP in Guillain-Barré syndrome, phantom limb pain, and spinal cord injury or cauda equina syndrome. A randomized controlled trial enrolling 165 patients with PDN found that mean daily pain and sleep interference scores, Patient and Clinician Global Impression of Change scores for pain, and Profile of Mood States were all improved in the gabapentin group compared with placebo. Mean daily pain and sleep interference scores, as well as quality of life measures, were improved by gabapentin in a randomized controlled trial enrolling 229 patients with postherpetic neuralgia. Gabapentin also reduced mean daily pain scores by 21% in a recent randomized controlled trial enrolling 305 patients with a wide range of NeP syndromes. Gabapentin was well tolerated in all of these clinical trials, with a relatively low rate of patient dropout.

Pregabalin

Two double-blind, placebo-controlled, randomized clinical trials showed that pregabalin (150–600 mg/day) significantly reduced pain in patients (n = 173 and 238, respectively) with postherpetic neuralgia. Moreover, patient’s sleep disturbances were attenuated and overall quality of life was improved with pregabalin treatment. In both studies, significant pain relief began during week 1 and lasted throughout the remainder of the trial (8 weeks).

In another randomized, double-blind, placebo-controlled, 8-week study of patients with PDN, pregabalin significantly decreased pain (P < 0.0001) throughout the duration of the study and was associated with improved mood, sleep disturbance, and quality of life. Patients (n = 146) with a history of 1 to 5 years of PDN were randomized to either placebo (n = 70) or pregabalin (n = 76)
The primary efficacy measure was the end point mean pain score, which was taken from daily patient dairies (11-point numerical pain rating scale). In the above studies, pregabalin, even at the highest dosage (600 mg/day), was well tolerated.

**Lamotrigine**

In an open trial, 14 patients with intractable sciatica had decreased pain scores and improved performance on the straight leg raise and lumbar spine range of motion tests after 4 weeks of lamotrigine 400 mg/day, the highest dosage used in the study. Lamotrigine treatment also reduced pain scores on a VAS and the McGill Pain Questionnaire (MPQ) in a randomized controlled trial enrolling 227 patients with HIV-associated neuropathies; the improvement compared with placebo treatment was statistically significant in the stratum of patients (n = 92) receiving neurotoxic antiretroviral therapy. In another randomized controlled trial, lamotrigine did not significantly reduce pain secondary to spinal cord injury in a total sample of 22 patients but did significantly reduce pain at or below the level of injury in those patients with incomplete spinal cord injury. Lamotrigine significantly reduced daily pain scores in 59 patients with PDN and 27 patients with central poststroke pain, 11 of 13 patients with refractory trigeminal neuralgia treated with lamotrigine in a randomized controlled trial experienced improvement on a composite index that included escape medication use, total pain scores, and global evaluations. Lamotrigine has been associated with severe rash, including Stevens-Johnson syndrome, in 0.3% of patients and less severe rash in approximately 10%. The risk for rash is reduced, however, when lamotrigine is started at a low dose and titrated slowly.

**Oxcarbazepine**

In a controlled trial that enrolled 24 patients with trigeminal neuralgia, both oxcarbazepine and its parent compound, carbamazepine, reduced pain and symptoms, and although higher doses of oxcarbazepine were required, it was better tolerated than carbamazepine. In a recent open-label trial enrolling 30 patients with PDN, oxcarbazepine reduced VAS and MPQ total pain and present pain intensity scores. Although oxcarbazepine is better tolerated than its parent compound, it appears to have higher rates of central nervous system and autonomic side effects than other recently developed AEDs.

**Topiramate**

Topiramate exhibited efficacy in 3 patients with intractable trigeminal neuralgia in a preliminary study but not in a confirmatory follow-up evaluation. In 97 children who frequently experienced migraine headaches, topiramate decreased the mean headache frequency, severity, and duration. Topiramate has a relatively high rate of cognitive side effects and weight loss.

**Zonisamide**

Zonisamide has not yet been evaluated in a clinical trial of patients with NeP; however, in an open-label study, zonisamide relieved radiculopathy-associated NeP by 30% to >60% in 18 of 40 patients. Two patients dropped out of the study because of drowsiness. In an open-label prospective study in 55 patients with a variety of chronic, refractory NeP conditions, zonisamide reduced daily pain scores by more than 50% in 15 of 42 evaluable patients (35.7%) and by 25% to 50% in 10 (23.8%).
Levetiracetam
Levetiracetam was fully or partially effective in improving sleep and reducing allodynia and the size of the painful area in 6 of 10 patients with postherpetic neuralgia. All patients in this trial had been treated unsuccessfully with other agents, including gabapentin.\textsuperscript{167} A retrospective chart review study found that levetiracetam was effective or very effective as prophylaxis for adult migraine headaches in 11 of 20 patients.\textsuperscript{168}

Felbamate
Felbamate has not been evaluated in a clinical trial for NeP. There are case reports of felbamate-induced relief of trigeminal neuralgia, but bone marrow and liver toxicity and a lack of data from controlled trials have limited enthusiasm for this AED as a treatment for NeP.\textsuperscript{77}

Tiagabine
Tiagabine has not been evaluated in a clinical trial for NeP. Tiagabine was effective in a small open-label pilot study of 17 patients with painful sensory neuropathy.\textsuperscript{169} Only 9 patients completed the study, and there appeared to be an inverse relationship between tiagabine dose and pain reduction.

Summary
Neuropathic pain is characterized by symptoms that vary considerably from patient to patient and a complex etiology that involves structural and functional changes in damaged and undamaged portions of the peripheral and central nervous systems. Pathologic mechanisms thought to contribute to NeP include changes in the anatomy and function of primary afferent axons and DRG neurons and remodeling in the spinal dorsal horn. Hyperexcitability of pain afferents, cross-talk between pain afferents and sympathetic and/or large-diameter touch fibers, and an overall increase in ascending pain signals are all involved in the development and maintenance of NeP. Altered modulatory actions of central and peripheral neuropeptides that are up-regulated in NeP may also contribute to neuronal hyperexcitability. Many agents that have been used effectively for the treatment of nociceptive pain are much less effective in patients with NeP. Newer AEDs modulate ion channel function and modify the actions of neurotransmitters involved in pain processing. Recent results from controlled clinical trials have suggested considerable promise for several of these agents in patients with NeP.

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REFERENCES


123. Xu XJ, Hao JX, Seiger A, Wiesenfeld-Hallin Z. Systemic excitatory amino acid receptor antagonists of the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor and of the N-methyl-d-aspartate (NMDA) receptor relieve mechanical hypersensitivity after transient spinal cord ischemia in rats. J Pharmacol Exp Ther 1993;367:140–144.


**Figure legends**

Figure 1. Sites of action for different NeP therapies. NE = norepinephrine; 5-HT = serotonin; AED = antiepileptic drug; NMDA = N-methyl-D-aspartate; GABA = γ-aminobutyric acid. Adapted from Dickenson 2002, reference 16.

Figure 2. Changes in neuronal transmission thought to be involved in the development of NeP. Adapted from Woolf 1999, reference 19.

Figure 3. Aβ-, Aδ-, and C-fibers converge on a range of neurons within multiple laminae of the dorsal horn of the spinal cord. The wide range of neuronal innervation may underlie the sensitization that occurs with allodynia. Adapted from Jessell and Kelly 1991, reference 43.
Table 1

**Mechanisms Involved in NeP and Related Symptoms and Therapeutic Targets**

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</table>

Abbreviations: DRG = dorsal root ganglion; AEDs = antiepileptic drugs; MS = multiple sclerosis.
Adapted from Woolf 1999, reference 21.
Table 2

**Mechanism of Action of New AEDs With Potential Use for NeP Treatment**

<table>
<thead>
<tr>
<th>AED</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin / pregabalin</td>
<td>Bind to α₂* subunit of VDCCs and inhibit calcium influx; decrease glutamate and norepinephrine, but increase GABA neurotransmission</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Binds to and inhibits sodium channels; inhibits R-type VDCCs; decreases glutamate release; stabilizes neuronal membranes</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Binds to and inhibits sodium channels; blocks L-type VDCCs; suppresses action potentials</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Decreases sodium currents; decreases calcium influx via AMPA/kainate antagonism; GABA agonist</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Blocks sodium and T-type VDCCs; serotonin, dopamine agonist; inhibits release of nitric oxide; free radical scavenger</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Inhibits N-type VDCCs; suppresses action potentials; inhibits delayed rectifier potassium current</td>
</tr>
<tr>
<td>Felbamate</td>
<td>Binds to NMDA receptor channel and decreases NMDA currents; blocks sodium and calcium channels; decreases glutamate release; GABA agonist</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>Binds to GABA transporter (GAT1) to inhibit GABA reuptake; potentiates GABA (A+B) currents</td>
</tr>
</tbody>
</table>

Abbreviations: AED = antiepileptic drug; VDCCs = voltage-dependent calcium channels; GABA = γ-aminobutyric acid; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; NMDA = N-methyl-D-aspartate; GAT1 = GABA uptake transporter 1.

Adapted from Jensen 2002 reference 77; LaRoche 2004 reference 78.
### Clinical Trials of New AEDs in the Management of NeP

<table>
<thead>
<tr>
<th>Drug</th>
<th>Patients enrolled</th>
<th>Study design</th>
<th>Type of NeP</th>
<th>Treatment duration</th>
<th>Primary outcome measure</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin$^{147}$</td>
<td>31</td>
<td>Open-label</td>
<td>Spinal cord injury</td>
<td>8 weeks</td>
<td>VAS pain and sleep interference scores</td>
<td>Decreased scores in patients with &lt;6 months injury duration</td>
</tr>
<tr>
<td>Gabapentin$^{145}$</td>
<td>18</td>
<td>DB, R, P1, CO</td>
<td>Guillain-Barré syndrome</td>
<td>2 weeks</td>
<td>Numeric pain rating, sedation score, fentanyl use, adverse effects</td>
<td>Decreased scores in all measures</td>
</tr>
<tr>
<td>Gabapentin$^{146}$</td>
<td>19</td>
<td>DB, R, PC, CO</td>
<td>Phantom limb pain</td>
<td>6 weeks</td>
<td>VAS pain intensity difference scores</td>
<td>Gabapentin &gt; P1, $P = 0.03$</td>
</tr>
<tr>
<td>Gabapentin and amitriptyline$^{151}$</td>
<td>28</td>
<td>DB, R, CO</td>
<td>PDN</td>
<td>6 weeks</td>
<td>PD – 13-word list of verbal descriptors</td>
<td>Both drugs decreased pain scores</td>
</tr>
<tr>
<td>Gabapentin and amitriptyline$^{152}$</td>
<td>25</td>
<td>R, Open-label</td>
<td>PDN</td>
<td>12 weeks</td>
<td>Pain and parasthesia scores</td>
<td>Gabapentin &gt; Amitriptyline, $P &lt; 0.05$</td>
</tr>
<tr>
<td>Gabapentin$^{148}$</td>
<td>165</td>
<td>DB, R, PC, MC</td>
<td>PDN</td>
<td>8 weeks</td>
<td>11-point Likert scale</td>
<td>Gabapentin &gt; P1, $P &lt; 0.001$</td>
</tr>
<tr>
<td>Gabapentin$^{149}$</td>
<td>229</td>
<td>DB, R, PC</td>
<td>PHN</td>
<td>8 weeks</td>
<td>11-point Likert scale</td>
<td>Gabapentin &gt; P1, $P &lt; 0.001$</td>
</tr>
<tr>
<td>Drug</td>
<td>N</td>
<td>Study Design</td>
<td>Condition</td>
<td>Duration</td>
<td>Measure</td>
<td>Results Description</td>
</tr>
<tr>
<td>-----------------</td>
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<td>-------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>305</td>
<td>DB, R, PC</td>
<td>A wide range of NeP syndromes</td>
<td>8 weeks</td>
<td>PD – change in average score (baseline versus final week)</td>
<td>Gabapentin &gt; P1, $P = 0.048$</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>173</td>
<td>DB, R, PC</td>
<td>PHN</td>
<td>8 weeks</td>
<td>Mean of the last 7 daily pain ratings</td>
<td>Greater decreases in pain than patients treated with placebo</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>238</td>
<td>DB, R, PC</td>
<td>PHN</td>
<td>8 weeks</td>
<td>End point mean pain scores</td>
<td>$\geq 50%$ decrease in mean pain score from baseline to end point</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>146</td>
<td>DB, R, PC</td>
<td>PDH</td>
<td>8 weeks</td>
<td>End point mean pain score from daily patient diaries</td>
<td>Significant improvements vs placebo for mean pain scores, $P &lt; 0.0001$</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>14</td>
<td>Open-label</td>
<td>Intractable sciatica</td>
<td>4 weeks</td>
<td>Spontaneous pain, short form MPQ, Straight Leg Raise test, range of motion of lumbar spine</td>
<td>All measures improved, but significantly only at the highest dose used (400 mg/day)</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>227</td>
<td>DB, R, PC</td>
<td>HIV-associated painful NeP</td>
<td>11 weeks</td>
<td>Gracely pain scale, VAS, MPQ, global impression scales</td>
<td>Lamotrigine &gt; P1 for all measures, $P \geq 0.02$</td>
</tr>
<tr>
<td>Study</td>
<td>Participants</td>
<td>Intervention</td>
<td>Follow-up</td>
<td>Outcome</td>
<td>Result</td>
<td></td>
</tr>
<tr>
<td>-------</td>
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</tr>
<tr>
<td>Lamotrigine(^{158})</td>
<td>30 DB, R, PC, CO</td>
<td>Spinal cord injury</td>
<td>9 weeks</td>
<td>Change in median pain score (baseline versus final week)</td>
<td>Lamotrigine &gt; P1 only for patients with incomplete spinal cord injury</td>
<td></td>
</tr>
<tr>
<td>Lamotrigine(^{159})</td>
<td>59 R, Pl</td>
<td>PDN</td>
<td>6 weeks</td>
<td>Numerical pain sale</td>
<td>Lamotrigine &gt; Pl, (P &lt; 0.001)</td>
<td></td>
</tr>
<tr>
<td>Lamotrigine(^{160})</td>
<td>30 DB, R, PC, CO, MC</td>
<td>Central post-stroke pain</td>
<td>8 weeks</td>
<td>Mean daily pain score</td>
<td>Lamotrigine &gt; P1, (P = 0.01)</td>
<td></td>
</tr>
<tr>
<td>Lamotrigine(^{161})</td>
<td>14 DB, PC, CO</td>
<td>TN</td>
<td>2 weeks</td>
<td>Composite efficacy index including usage of escape medication, total pain scores, and global evaluations</td>
<td>Lamotrigine &gt; P1, (P = 0.011)</td>
<td></td>
</tr>
<tr>
<td>Oxcarbazepine and carbamazepine(^{162})</td>
<td>24 Open-label</td>
<td>TN</td>
<td>—</td>
<td>Pain scores</td>
<td>Both drugs relieved symptoms</td>
<td></td>
</tr>
<tr>
<td>Oxcarbazepine(^{163})</td>
<td>30 Open-label</td>
<td>PDN</td>
<td>9 weeks</td>
<td>VAS, short form MPQ</td>
<td>Oxcarbazepine &gt; P1, (P = 0.0001)</td>
<td></td>
</tr>
<tr>
<td>Topiramate(^{164})</td>
<td>3 DB, R, PC, CO</td>
<td>TN</td>
<td>—</td>
<td>Pain scores</td>
<td>Topiramate &gt; P1, (P = 0.04)</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>N</td>
<td>Study Design</td>
<td>Study Population</td>
<td>Duration</td>
<td>Outcome Measures</td>
<td>Result</td>
</tr>
<tr>
<td>--------------</td>
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<td>--------------</td>
<td>-------------------</td>
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<td>----------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Topiramate</td>
<td>97</td>
<td>Open-label</td>
<td>Pediatric migraine</td>
<td>≥12 weeks</td>
<td>Headache frequency, severity, duration, headache-related disability</td>
<td>Topiramate &gt; P1 in all measures, <em>P</em> &lt; 0.05</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>55</td>
<td>Open-label, prospective</td>
<td>Chronic, refractory NeP</td>
<td>≥12 weeks</td>
<td>PD - daily pain scores</td>
<td>&gt;50% reduction in 15 of 42 evaluable patients; 25%-50% in 10</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>10</td>
<td>Open-label, prospective</td>
<td>PHN</td>
<td>≥12 weeks</td>
<td>Size of painful area, measures of allodynia, sleep interference</td>
<td>Levetiracetam was fully or partially effective in 6 patients</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>20</td>
<td>Retrospective analysis</td>
<td>Adult migraine</td>
<td>6-30 weeks</td>
<td>Headache frequency, severity, duration rated on a global scale</td>
<td>Levetiracetam was very effective in 11 patients and modestly effective in 7</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>17</td>
<td>Open-label, pilot study</td>
<td>Painful sensory NP</td>
<td>4 weeks</td>
<td>MPQ (baseline versus week 4), quantitative sensory testing</td>
<td>Tiagabine &gt; no treatment, <em>P</em> &lt; 0.03</td>
</tr>
</tbody>
</table>

Abbreviations: DB = double-blind; R = randomized; CO = crossover; P1 = placebo; PC = placebo-controlled; MC = multicenter; NeP = neuropathy; PDN = painful diabetic neuropathy; PHN = postherpetic neuralgia; PD = pain diary; TN = trigeminal neuralgia; VAS = visual analog scale; MPQ = McGill pain questionnaire; HADS = hospital anxiety and depression score.
Figure 1
Figure 2
Figure 3
Calcium and Sodium Channel Antagonists for the Treatment of Pain

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Calcium and Sodium Channel Antagonists for the Treatment of Pain

Mark S. Wallace, M.D.
Professor of Clinical Anesthesiology

INTRODUCTION

Several lines of evidence developed in preclinical models suggest that both spontaneous and evoked pain is mediated in part by voltage-sensitive sodium and calcium channels. Sodium and calcium channel antagonists used in clinical practice are of the voltage-dependent type in that the neurons must remain depolarized for a significant period of time for maximal blocking action to occur. This is in contrast to the effects of tetrodotoxin on the sodium channel which is independent of the conformational state of the channel. Both the central and peripheral nervous system has an abundance of sodium and calcium channels (Taylor, 1996).

There are many subtypes of sodium channels expressed throughout the nervous system. Blockade of the sodium channel prevents the upstroke of the axonal action potential. If this blockade occurs in pain-sensitive sensory neurons, pain relief may result. It is thought that certain pain-sensitive peripheral sensory neurons express a distinct type of tetrodotoxin-insensitive sodium channel (Akopian et al, 1996). Unfortunately, all of the existing agents are not selective for this distinct sodium channel which limits their utility in the management of pain. The exact site of action of the sodium channel antagonists is unclear.

There are six unique types of calcium channels expressed throughout the nervous system (designated L, N, P, Q, R and T) (Bean 1989; Hess 1990; Swandulla et al, 1991). It is well known that voltage-sensitive calcium channels of the N-type exist in the superficial laminae of the dorsal horn and are thought to modulate nociceptive processing by a central mechanism (Gohil et al, 1994). Blockade of the N-type calcium channel in the superficial dorsal horn modulates membrane excitability and inhibits neurotransmitter release resulting in pain relief (Augustine et al 1987). Ziconotide, a 25-amino acid peptide that is a synthetic version of a naturally-occurring peptide found in the venom of the marine snail, Conus magus, specifically and selectively binds to N-type voltage-sensitive calcium channels (Olivera et al, 1985, Aosaki and Kasai 1989; Sher and Clementi 1991). It is the first and only N-type calcium channel antagonist to enter clinical development.

EFFECTS OF THE SODIUM AND CALCIUM CHANNEL ANTAGONISTS ON NOCICEPTIVE PROCESSING

Based on preclinical studies, the processing of nociceptive information may be characterized in terms of several discrete mechanisms. These mechanisms reflect: 1) the processing of acute nociceptive input; and 2) facilitated states which arise from persistent afferent input (as after tissue injury), and (3) altered processing which arises secondary to nerve injury, both yielding anomalous states of hyperalgesia and allodynia. There is an abundance of research on the effects of the sodium and calcium channel antagonists on these different mechanisms of nociceptive processing.
Effects on acute nociceptive processing

In humans, skin temperatures above 33°C or below 30°C will evoke an initial report of warmth or coolness, respectively. At further extremes of temperature, the subject reports the stimulus as painful, with the magnitude of the pain state being proportional to the stimulus intensity (Verdugo and Ochoa, 1992). A low intensity mechanical stimulus yields a sensation of touch, while higher intensities leading to physical distortion/injury will yield a report of pain, with the magnitude of the pain state being proportional to the stimulus intensity (Raja et al, 1988). The correlation between sensation and nerve fiber activity has been extensively studied. Fascicular recording and compression-ischemia block have shown that low-threshold tactile sensations are subserved by large myelinated fibers (Aβ), cool sensation by small myelinated fibers (Aδ), and warmth and pain by small unmyelinated fibers (C-fibers) (Yarnitsky and Ochoa, 1990 and 1991; Ochoa and Torebjork, 1983 and 1989; Torebjork et al, 1987) Large myelinated fiber function can be assessed with mN (milliNewtons) of pressure applied to the skin (Gruener and Dyck, 1994); small myelinated fiber function can be assessed with quantitative thermal sensory testing and small unmyelinated fiber function can be assessed with quantitative thermal sensory testing and mechanical pain (pressure/pinch algometer) (Verdugo and Ochoa, 1992). These are the premises that established the models used to study the effects of analgesics on neurosensory processing. Specifically, the effects of the sodium and calcium channel antagonists on these experimental models of acute nociceptive processing will be discussed below.

Sodium Channel Antagonists While direct application of lidocaine to a nerve results in axonal conduction block, systemic delivery can exert potent effects upon sensory processing at doses which do not produce conduction block. At plasma lidocaine concentrations of up to 3 mg/ml, there are no prominent effects on acute heat, cold, or mechanical thresholds (Wallace et al, 1997, Bach et al, ). A similar lack of effect on acute nociceptive processing has been demonstrated with mexiletine, an oral bioavailable analog of lidocaine, at plasma concentrations of up to 0.5 mg/ml (Ando et al, 1999). Two other studies have demonstrated a significant effect of intravenous lidocaine on acute ischemic pain (Boas et al, 1982; Rowlingson et al, 1980). However, the plasma concentrations were above 3 mg/ml plasma level which exceed the maximal tolerable dose (see side effects below). This lack of effect of intravenous lidocaine upon acute thermal and mechanical stimuli appears different from several previous observations. First, the lack of a robust effect of intravenous lidocaine on acute neurosensory thresholds is somewhat inconsistent with preclinical findings showing a depressed conduction velocity in C fibers and to a lesser extent Aδ fibers after intravenous lidocaine though the difference suggests that these modest changes may not relevant to detection thresholds (Woolf, 1995; Tanelian and MacIver, 1991; DeJong and Nace 1968). Secondly, previous human studies have evaluated the effects of intravenous lidocaine on perception thresholds for electrocutaneous stimulation. The three different frequencies used: 2000, 250 and 5 are thought to recruit at threshold intensities progressively smaller afferent populations (Aβ, Aδ and finally C fibers) as stimulation frequency is lowered (Katims et al, 1986; Masson and Boulton, 1991). In those studies, lidocaine appeared to elevate threshold for the 250 and 5 Hz, but not the 2000 Hz stimuli. Inspection of the data, however, emphasize that the repeated epochs of stimulation at 250 and 5 hz were associated with a progressive decrease in threshold, which may either reflect the initiation of a facilitated state or habituation to the stimulus. It may be the facilitated component evoked by small afferent stimulation that is being affected by the intravenous lidocaine. In contrast, lamotrigine and phenytoin, two sodium channel antagonists with anticonvulsant properties, have been shown to decrease acute pain induced by the cold pressor.
test. The effect of lamotrigine on acute pain suggests a superior effect over mexiletine and lidocaine and therefore other studies are warranted.

**Calcium Channel Antagonists** Although the calcium channel antagonists have not been studied on acute nociceptive processing in humans, there are studies which have demonstrated a significant reduction of the response to the hot-plate in the rat (Malmberg and Yaksh, 1995). This is in contrast to the sodium channel antagonists which have not been demonstrated to affect acute pain in animal models (i.e. hot-plate, tail-flick) suggesting that the N-type calcium channel antagonists have a greater analgesic potency (Hunter et al, 1997)

**Effects on facilitated pain processing**

Following tissue injury, a persistent activity is noted in sensory C fibers (Dickenson and Sullivan, 1987c). This persistent C fiber activity yields a facilitated state in spinal wide dynamic range (WDR) neurons characterized by an enlarged receptive field and an exaggerated discharge in response to subsequent Aβ and C fiber activity (Mendell and Wall 1965; Dickenson and Sullivan, 1987a; Woolf and Chong, 1993 for references). A local injury (such as a burn or incision) or injection of irritants (formalin or capsaicin) results in a persistent low level afferent discharge and an associated behaviorally defined hyperalgesia (see Yaksh, 1997).

**Sodium Channel Antagonists** In animals, the systemic delivery of lidocaine and mexiletine in concentrations that do not block axon conduction will reduce facilitated spinal processing induced by tissue injury (Tanelian and Maclver, 1991; Kamei et al, 1993; Jett et al, 1997). The central facilitation induced by spinal delivery of a glutamate agonist is blocked by IV lidocaine (Biella and Sotgui, 1993 a,b) and the central release of substance P is inhibited by systemic mexiletine (Kamei et al, 1992), indicating a central action. However, the mg/kg dose administered in these studies are much higher than the maximal tolerable dose in humans making it difficult to interpret clinically.

In humans, IV lidocaine has been demonstrated to significantly reduce postoperative pain with achieved plasma levels of 1-2 mg/ml (Cassuto et al, 1985; Bartlett and Hutasurani, 1961). In addition, lamotrigine significantly reduces the analgesic requirements of postoperative pain (Bonicalzi et al, 1997). Both systemic lidocaine and mexiletine have minimal effects on the secondary hyperalgesia induced by intradermal capsaicin (Wallace et al, 1997; Ando et al, 1999). With both agents there is a significant reduction in the capsaicin induced flare response and corresponding heat hyperalgesia. In contrast, the opioids and NMDA receptor antagonists have a significant effect on capsaicin induced secondary hyperalgesia and no effect on the flare response. This suggests a peripheral mechanism of action of the sodium channel antagonists which may explain the disappointing clinical efficacy in neuropathic pain (see below). However, these findings suggest that studies are needed on the effects of the sodium channel antagonists on the pain of neurogenic inflammation (i.e. rheumatoid arthritis). This also explains the efficacy of the sodium channel antagonists on postoperative pain as opposed to neuropathic pain. Postoperative pain involves a peripheral receptor activation whereas neuropathic pain involves axonal, dorsal root ganglion, or dorsal horn activation.

**Calcium Channel Antagonists** The calcium channel antagonists have been shown to be effective in both the formalin and acute arthritis model in the rat (Malmberg and Yaksh, 1995; Bowersox et al, 1996; Sluka, 1998). As with the opioids, calcium channel antagonists significantly affect both phase I and phase II of formalin induced hyperalgesia; however, there is no development of tolerance with chronic infusions of up to 7 days as is seen with the opioids (Malmberg and
Yaksh, 1995). Blockade of non-N type calcium channels have no effect on animal models of facilitated pain (Malmberg and Yaksh, 1994).

Ziconotide is currently in Phase III trials for the treatment of postoperative pain. A pilot study of 24 patients undergoing orthopedic and lower abdominal surgery showed a significant reduction in intravenous morphine consumption with the continuous infusion of 7 mg/hr of epidural Ziconotide. The side effect and safety profile was very good (Atanassoff et al, 1998). There is currently a large Phase III trial in progress on the efficacy of Ziconotide in postoperative pain. Preclinical and clinical trials are promising on the efficacy of Ziconotide for acute postoperative pain.

Effects on neuropathic pain

Neuropathic pain which results from nervous system injury is often debilitating and refractory to treatment. Neuropathic pain may display several characteristics including: 1) an ongoing sensation described as unpleasant (dysesthesia); 2) an exaggerated pain response to a given noxious stimulus (hyperlgesia); and/or 3) a report of pain secondary to a non-painful stimulus (allodynia, both thermal and mechanical). In addition, neuropathic pain is often described as electric shock-like sensations and spontaneous burning pain.

Sodium Channel Antagonists Several lines of evidence suggest that both the spontaneous and evoked pain after nervous system injury is mediated in part by an increase in the density of voltage-sensitive sodium channels in the injured areas of the axon and dorsal root ganglion of the injured axon (Cummins and Waxman, 1997; England et al, 1996; England et al, 1994; Devor et al, 1993). In animal models of neuropathic pain, it has been demonstrated that spontaneous and evoked pain is significantly diminished after delivery of sodium channel antagonists (Jett et al, 1997; Kamei et al, 1992; Xu et al, 1992; Chabal et al, 1989). Importantly, these effects occur at plasma concentrations that do not produce an afferent conduction block (Devor et al, 1992).

Lidocaine and Mexiletine have been the most widely studied in the treatment of neuropathic pain. When examined in patients reporting significant pain secondary to a variety of neuropathic states, subanesthetic doses of systemic lidocaine produce clinically relevant relief in diabetes (Bach et al, 1990; Kastrup et al, 1987), nerve injury pain states (Marchettini et al, 1992; Rowbotham et al, 1991), and in cancer (Tanelian and Brose, 1991). These results suggest in humans, as in animals, that after nerve injury sodium channels mediate a substantive facilitation of afferent processing. A recent study by Wallace et al showed minimal effects of intravenous lidocaine on pain and allodynia of complex regional pain syndrome type I and II with plasma levels of up to 3 mg/ml plasma level (Wallace et al, 2000). Mexiletine has been reported to be effective in a variety of neuropathic pain syndromes including diabetic neuropathy (Stracke et al, 1992; Dejgard et al, 1988), alcoholic neuropathy (Nishiyama and Sakuta, 1995; Nishiyama et al, 1990), peripheral nerve injury (Davis, 1993; Chabal et al, 1992; Tanelian and Brose, 1991), and thalamic pain (Awerbuch and Sandyk, 1990). However, more recent reports question the efficacy of oral mexiletine in neuropathic pain (Chong et al, 1997; Wright et al, 1997; Chiu-Tan et al, 1996) and although the study by Stracke et al showed a significant decrease in specific components of neuropathic pain, they did not show any significant effect on pain scores. A recent study by Wallace et al failed to show a significant effect on allodynia or pain after nerve injury with doses of mexiletine of up to 900mg/day (Wallace et al, submitted for publication). It appears that oral mexiletine is a poor choice for the management of neuropathic pain with a prominent allodynia. The exact therapeutic plasma concentration for analgesia is yet
to be determined, but it appears that dose-limiting side effects occur at a lower plasma concentration than analgesia (Wallace et al submitted for publication; Ando et al, submitted for publication). Lidocaine appears to be a better choice but is limited to intravenous delivery.

Lamotrigine is a new sodium channel antagonist with activity at glutaminergic sites. It has been shown to decrease the cold allodynia in nerve constriction models (Hunter et al, 1997) and induced analgesia in the model of chronic hyperalgesia in streptozotocin-induced diabetic rats (Nakamura-Craig and Follenfant, 1995). Clinically, it has been demonstrated to significantly decrease the pain of refractory trigeminal neuralgia (Zakrzewska et al, 1997) and there are several case reports on efficacy in neuropathic pain (Harbison et al, 1997; di Vadi and Hamann, 1998; Canavero and Bonicalzi, 1996). There is one double-blind placebo controlled study which showed no effect in neuropathic pain at doses of up to 200 mg/day (McCleane, 1999). Lamotrigine is well tolerated and therapeutic levels for analgesia are yet to be determined.

**Calcium Channel Antagonists** Many preclinical studies have demonstrated the efficacy of Ziconotide on nerve injury induced mechanical allodynia (Bowersox et al, 1996; White and Cousins, 1998; Xiao and Bennet, 1995). The first clinical report on the use of Ziconotide for neuropathic pain was by Brose et al who described a patient with refractory pain secondary to brachial plexus avulsion injury who responded to intrathecal Ziconotide (Brose et al, 1997). There is one double-blind, placebo controlled study on intrathecal Ziconotide on refractory neuropathic pain. Two hundred and fifty-nine patients with a wide variety of neuropathic pain syndromes were enrolled. Intrathecal Ziconotide resulted in a significant reduction of pain over placebo (Presley et al, 1998). Intrathecal Ziconotide is currently in phase III trials for the management of neuropathic pain.

**Side Effects**

It is clear that if therapeutic levels of the sodium and calcium channel antagonists are achieved, pain relief occurs. However, because of the non-specificity of these channel antagonists, multiple channel subtype blockade occurs throughout the nervous system which results in dose-limiting side effects.

**Sodium channel antagonists** The correlation between plasma levels and side effects has been studied the most with intravenous lidocaine (Table I). It appears that the maximally tolerated plasma level of lidocaine is around 3 mg/ml which is plasma level that we begin to see analgesia (Wallace et al, 1997; Wallace et al, 2000). The most common side effects of mexiletine are nausea, tremors, and irritability which are dose related (Manolis, 1990). It appears that the maximum tolerable dose of mexiletine is between 800 - 900 mg/day (Galer et al, 1996; Wallace et al, submitted for publication). However, it is questionable if this dose results in analgesic plasma levels. The highest tolerated plasma mexiletine level is about 0.5 mg/ml which is below the analgesic level (Wallace et al, submitted for publication).

**Calcium channel antagonists** The N-type calcium channel antagonists have both spinally and supraspinally mediated side effects. A recent study on intrathecally administered Ziconotide for neuropathic pain reported the following side effects: dizziness, nausea, nystagmus, gait imbalance, confusion, constipation and urinary retention (Presley et al, 1998). All of these side effects resolved upon dosage reduction or discontinuation. Another study on the short term epidural delivery of Ziconotide for postoperative pain did not
report these side effects (Atanassoff et al, 1998). It appears that spinally delivered Ziconotide has a narrow therapeutic window. When this therapeutic window is achieved, analgesia is possible without unacceptable side effects.

Conclusions

This review demonstrates mixed results on the efficacy of the sodium channel antagonists for the treatment of neuropathic pain. Early studies on the N-type calcium channel antagonists are promising for both acute and chronic pain. Future studies should be directed at better identifying the subtypes of sodium and calcium channels located on pain-sensitive nerve fibers thereby allowing for more specific drugs directed at these channels. This should result in better pain relief without dose-limiting side effects.
<table>
<thead>
<tr>
<th>Side effect</th>
<th>Plasma level μg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Lightheadedness</td>
<td>1-2</td>
</tr>
<tr>
<td>2) Periorbital numbness</td>
<td>2</td>
</tr>
<tr>
<td>3) Metallic taste</td>
<td>2-3</td>
</tr>
<tr>
<td>4) Tinnitus</td>
<td>5-6</td>
</tr>
<tr>
<td>5) Blurred vision</td>
<td>6</td>
</tr>
<tr>
<td>6) Muscular twitching</td>
<td>8</td>
</tr>
<tr>
<td>7) Convulsions</td>
<td>10</td>
</tr>
<tr>
<td>8) Cardiac depression</td>
<td>20-25</td>
</tr>
</tbody>
</table>
REFERENCES


13. Bowersox, SS; Gadbois, T; Singh, T; Pettus, M; Wang, YX; Luther, RR. Selective N-type neuronal voltage-sensitive calcium channel blocker, SNX-111, produces spinal antinociception in rat models of acute, persistent and neuropathic pain.


42. Malmberg, AB; Yaksh, TL. Voltage-sensitive calcium channels in spinal nociceptive processing: blockade of N- and P-type channels inhibits formalin-induced nociception. Journal of Neuroscience, 1994, 14:4882-90

47. Nakamura-Craig, M; Follenfant, RL. Effect of lamotrigine in the acute and chronic hyperalgesia induced by PGE2 and in the chronic hyperalgesia in rats with streptozotocin-induced diabetes. Pain, 1995, 63:33-7


62. Tanelian DL, Brose WG: Neuropathic pain can be relieved by drugs that are use-dependent sodium channel blockers: lidocaine, carbamazepine, and mexiletine. Anesthesiology 1991; 74:949-51


INTRATHecal DRUG DELIVERY FOR NON-CANCER PAIN

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Intrathecal Drug Delivery for Non-cancer Pain

Introduction

Clinical insight garnered from trends in patient response to initial conservative treatments for moderate-to-severe pain of noncancer origin has facilitated pharmacologic and technological advances in pain management over the past few decades. As a more recent application within the pain treatment continuum (Krames 1997), intrathecal (IT) drug delivery systems offer a functional alternative for the long-term management of select patients with intractable pain associated with various disease states, including failed back surgery syndrome, complex regional pain syndrome, spinal stenosis, osteoporosis with compression fractures, and peripheral neuropathies (Deer 2004). In contrast to other noninvasive therapeutic strategies for pain, IT drug delivery improves efficacy and tolerability through the employment of innovative techniques; a drug delivery pump contains and delivers analgesic medication to the spinal receptors through a connected catheter strategically placed into the cerebral spinal fluid. The site of action within the cerebrospinal fluid is influenced by the catheter location and the lipophilicity of the selected IT agent. Clinical benefit is achieved by an increased pharmacologic effect attributable to direct impact at the cellular level and avoidance of the blood brain barrier, while patients gain the advantage of greater independence and lower risk of infection than with external or partially externalized systems (Wallace).

Guided by the expertise of a skilled physician, the placement of the device is technically straightforward and confers minimal risks (Krames 1996). Despite use of preventive measures, perioperative complications including infection, bleeding, or drug mishaps have been associated with the procedure (Krakovsky 2007). Additional post-implantation adverse outcomes, such as failure to produce acceptable pain relief or improvement in function, can be minimized through rigorous patient selection and the use of tailored drug algorithms (Deer 2007).

Patient selection for treatment with IT drug delivery remains empiric and varies widely among practitioners. Nonetheless, there are numerous clues in the available scientific literature that may well guide the standardization of patient selection for IT therapy, an intervention typically considered after exhaustion of more conservative means of treatment. Assessment and grading of medical comorbidities, psychologic status, associated social, technical, and economic issues; favorable response to neuraxial trialing; absence of localized infection at the implant site; and lack of uncontrolled bleeding disorders have also been suggested as key elements of optimal patient selection (Krames 1996; Knight 2007). The purpose of this manuscript is to use experience- and knowledge-based expert opinion to systematically evaluate the available evidence for selecting patients suffering with chronic noncancer pain and assemble consensus guidelines aimed at optimizing patient selection for IT therapy.
References

Overview of Clinical Experience
Advances in intrathecal therapy (IT) have offered an alternative means to provide pain relief for patients inadequately relieved by standard medical management, as well as for those who cannot tolerate the adverse effects of high dose enteral or parenteral therapy (Smith 2008). Much has been published on IT, and the established literature may provide insight to therapeutic successes and outcomes of pain relief. These data can also be used to understand potential clinical complications of therapy, including challenges associated with dose escalation. When considering an individualized, multidimensional approach to patient selection, revisiting the published literature is essential to establish the risk/benefit ratio required to develop appropriate guidelines for long-term therapy.

Therapeutic Success and Outcomes of Pain Relief. Over the past decade, numerous prospective and/or randomized-controlled trials have evaluated the use of the intrathecal infusion modality in patients with noncancer pain in a variety of settings and patient populations (Table) (Hassenbusch 1991, Angel 1998, Anderson 1999, Kumar 2001, Thimineur 2004, Deer T 2004). Frequently used to treat pain attributed to failed back syndrome, complex regional pain syndrome, postherpetic neuralgia, or peripheral neuropathy, intrathecal therapy for noncancer pain has largely been found to reduce pain severity and evidence of analgesic response has been demonstrated in patients with neuropathic, visceral, deafferentation, or mixed pain (Hassenbusch 1991, Angel 1998, Anderson 1999, Kumar 2001, Thimineur 2004, Deer T 2004Winkelmuller 1996, Paice 1996). However, the variable nature of the agents used and patient populations included in these studies complicates the interpretation of data, as compared with other medical devices or anesthetic monotherapy. Furthermore, investigators often vary in how they administer drugs, with some using low flow, high flow, pulse infusion, or variable rates. Although many of these studies successfully replicate real-world practice, they do not allow for easy interpretation or for generalizations to be made across patient populations. More recently, specific drug and drug combinations have been studied as independent variables to better ascertain the effect of therapy (Staats 2004, Mironer 2001). In the absence of more definitive findings, practitioners
have largely relied on good clinical judgment to guide them through the patient selection process and long-term management (Krames 1997).

Despite widespread clinical use, a recent review of the available literature performed by Smith et al concluded that the role of implantable drug-delivery devices for the management of persistent noncancer pain remains uncertain (Smith 2008). Although an accumulation of data strongly supports the use of IT for cancer-related pain, additional trials are needed to determine the most appropriate pain conditions and/or subpopulation of patients with noncancer pain best suited for IT (Smith 2008). Regardless, the researchers found reasonably strong evidence supporting the short-term use of IT for treatment of cancer and neuropathic pain; evidence supporting the use of long-term therapy for intractable noncancer pain was not as robust (Smith HS 2008, Cohen SP 2007).

Clinical Implications of IT. Adverse effects and complications of therapy are also well documented in the literature. Studies have identified the emergence of issues related to dose escalation, specifically identifying intrathecal granulomas and excess mortality as potential consequences of intrathecal drug delivery (Smith 2008, Ghafoor, 2007, Deer 2008). To maximize the effects of treatment without compromising patient safety, it is essential that clinicians are aware of these potential adverse effects and recognize patients most at risk for complications of long-term IT (Ghafoor 2007).

The potential consequences of inappropriate dosing/titration were noted in the 2007 Interdisciplinary Polyanalgesia Conference recommendations (Deer 2008). Intrathecal therapy has been associated with severe adverse effects, including opioid-induced hyperalgesia, hypotension, sedation, and respiratory depression. Even more concerning, escalation of dosage that occurs too quickly can result in excess mortality (Belverud 2008). Acknowledging that most intrathecal agents have dose-related adverse effects, the panel recommended starting low and slowly increasing the dosage, as required, based on patient response. Notably, clinicians may consider accelerating dose changes in patients who are young and robust; however, caution should be used when titrating doses for those who are old and frail, adjusting administration only weekly. To further minimize the potential for adverse effects, the panel suggested that titration not exceed the recognized upper dosing limits for each agent (Deer 2008).

When dose escalation reaches its limit with monotherapy, clinicians have combined agents to provide continued analgesia. Based on data from animal studies, combination therapy demonstrates the potential to produce synergistic antinociception. Additionally, combination therapy may allow for lower dosages of each agent, thus reducing the possibility for adverse effects associated with higher administration rates. The safety and efficacy of combination therapy has been evaluated in many clinical studies, the findings of which support the combined use of opioids (morphine or hydromorphone) and bupivacaine, morphine and clonidine, and morphine and ziconotide for the treatment of noncancer pain (Deer 2008, Rainov NG, Wallace 2008).

For patients receiving high dosages of intrathecal medication, sudden cessation of drug—due to catheter disruption, battery failure, or human error—can also result in severe and sometimes fatal adverse effects (Jones 2005). Abrupt disruption of clonidine, for instance, can result in rebound hypertension and increase the risk for stroke in patients previously receiving high-dose therapy (Fitzgibbon D 1996, Smith 2008, Deer 2007). Baclofen withdrawal can also
be life-threatening, with reports of respiratory depression, hyperthermia, disseminated intravascular coagulation, acute renal failure, and acute multiorgan failure (Smith 2008, Ghafoor 2007).

Findings in the literature suggest that dose escalation contributes to the development of intrathecal granulomas. An online survey by Deer et al found catheter-tip inflammatory masses to be a relatively common occurrence, with 63.9% of respondents indicating that they had treated at least 1 patient who developed a granuloma secondary to IT (Deer 2009). In a review of published and unpublished case reports, Hassenbusch et al concluded that intrathecal granulomas occurred only in patients who received intrathecal opioids—alone or mixed with other agents—or in patients treated with agents that were not approved for long-term intrathecal delivery (Hassenbusch 2002). In fact, inflammatory masses have been attributed to the use of all agents used in implantable devices, with the exception of sufentaynl and fentanyl (Deer 2008). The relative frequency of granuloma development in noncancer patients may be the result of increased exposure to agents due to longer life expectancy and tendency to receive higher daily doses compared with cancer pain patients. Timely diagnosis of a catheter-tip inflammatory mass—symptoms of which include the loss of analgesic effect in addition to new and progressive neurologic symptoms—allows for minimally invasive therapy and may prevent the need for surgical removal of the mass (Hassenbusch 2002); if left untreated, intrathecal granulomas can lead to long-term neurologic damage and permanent paralysis (Ghafoor 2007).

**Patient Selection Guidelines.** A risk/benefit ratio can be extrapolated from the existing literature, focusing on both effective therapeutic interventions, as well as on the possible implications of therapy. Although practitioners will agree that proper patient selection is paramount to successful therapy, to date there is substantial variation in the ways in which IT candidates are chosen (Anderson 1999). Therefore, guidelines are needed to assist clinicians in selecting appropriate candidates for device implantation.
### Table. Prospective and Randomized IT Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Follow-up</th>
<th>Intervention</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hassenbusch et al (1991);</td>
<td>18 patients with neuropathic noncancer pain</td>
<td>0.8 to 4.7 years</td>
<td>Patients were treated with morphine sulfate or sufentanil citrate via an</td>
<td>61% of participants experienced good or fair pain relief at a mean 2.4 year follow up; average numeric</td>
<td>Neuropathic pain can be effectively treated with intrathecal opioids, although higher infusion</td>
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<tr>
<td>prospective observational</td>
<td></td>
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<td>implantable drug-delivery system</td>
<td>pain scores decreased by 39%; 5 of the 11 responders required lower opioid doses (12-24 mg/day</td>
<td>doses may be required</td>
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<td>morphine), whereas the remaining 6 patients required more than 34 mg/day morphine</td>
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<tr>
<td>Angel et al (1998);</td>
<td>11 patients with mixed or neuropathic noncancer pain</td>
<td>0.5 to 3 years (mean 2.3 years)</td>
<td>Patients received intrathecal morphine sulfate</td>
<td>73% of patients reported a good-to-excellent analgesic response; 27% of patients reported poor</td>
<td>Intrathecal morphine should be considered for intractable noncancer pain</td>
</tr>
<tr>
<td>prospective observational</td>
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<td></td>
<td>pain response</td>
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<tr>
<td>Anderson and Burchiel</td>
<td>30 patients with noncancer pain</td>
<td>2 years</td>
<td>Patients received intrathecal morphine sulfate; pharmacologic adverse</td>
<td>50% of patients reported at least a 25% reduction as measured by the visual analog scale</td>
<td>Continuous delivery of intrathecal morphine can be safe and effective for managing noncancer</td>
</tr>
<tr>
<td>(1999);</td>
<td>(50% had neuropathic-nociceptive pain; 33% had peripheral neuropathic pain;</td>
<td></td>
<td>effects were managed by a reduction in morphine dose, addition of</td>
<td></td>
<td>pain among carefully selected patients</td>
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<td></td>
<td>13% had deafferentation; and 3% had nociceptive pain)</td>
<td></td>
<td>bupivacaine, or switch to hydromorphone</td>
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<tr>
<td>Kumar et al (2001);</td>
<td>16 patients with noncancer pain, classified as nociceptive, mixed, or</td>
<td>1 to 4 years (mean 1.5 years)</td>
<td>Patients received morphine sulfate via an implantable drug-delivery system</td>
<td>The average pain relief was 67.5% after 6 months and 57.5% at last follow up; patients with</td>
<td>Intrathecal opioids are appropriate in carefully selected patients with noncancer pain</td>
</tr>
<tr>
<td>prospective observational</td>
<td>deafferentation pain</td>
<td></td>
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<td>deafferentation and mixed pain reported the best long-term results, with 75% and 61% reduction,</td>
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<td>respectively, as measured by the visual analog scale</td>
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<tr>
<td>Reference</td>
<td>Details</td>
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**Factors Related to Patient Selection**

*Spinal and Anatomical Technical Factors.* Safe and efficient access to the anatomical region of the spine is an indispensable procedural element of intrathecal drug delivery device implantation and outcome management (Deer 2009). However, recommended catheter insertion at the L2-3 or L3-4 level can be complicated by unique patient profiles and histories (Follett 2003); disease pathology, inherited or acquired medical characteristics, and associated anatomical variations in the spine require perioperative consideration to optimize surgical technique and device placement (Deer 2009). Metastatic involvement or occult pathology in the spinal column (Knight 2007), arthritis in the joints, paraplegia, spasticity, and scoliosis may impose restrictions on ideal patient positioning for the procedure, thereby requiring the determination of an alternate position to avoid compromising sterility and patient safety (Deer 2009). Fluoroscopy should be used in a compensatory effort to correct any residual anatomical tilt (Deer 2009). Anatomical variation may also impede recommended redirection of the catheter to
the intrathecal space for the final tip position (Deer 2009). Furthermore, abnormal anatomy may obscure recognition of the pressure gradient between the cerebrospinal fluid and the epidural space into the spinal fluid, which normally reduces the need for epidural test dosing and contrast imaging (Deer 2009). Other structures that merit procedure-related scrutiny include ligaments vital to the anatomical stability of the spine (ie, ligamentum flavum, anterior longitudinal ligament, and the posterior longitudinal ligament) (Deer 2009). Individual differences in nerve root size and volume contribute to variability in recovery rates from nerve injury; lower lumbar and sacral nerve roots are much larger than the lower thoracic nerve roots based on area and diameter of the root (Deer 2009). Special caution should be allotted to placement around the artery of Adamkiewicz—which varies in anatomical level of origin (from T8 to L3) and side of origin (supplying anterior thoracic spinal blood from the left side in 78% of individuals)—to avoid complications, such as paraplegia and other major neurologic sequelae (Deer 2009).

Arterial blood supply, cerebrospinal fluid bulk flow, and diffusion through the dura and meninges characterize anatomical factors that influence therapeutic outcomes through the uptake and delivery of intrathecal agents (Deer 2009). In particular, abnormal curvatures in vertebral column anatomy (eg, cervical lordosis and thoracic and sacral xiphosis) can impair drug spread and cerebrospinal circulation (Deer 2009). Cerebrospinal fluid volume fluctuations based on individual variations in height, physique, and abdominal pressure also impact analgesic efficacy; volume is significantly less than the normal mean volume of approximately 50 mL (from the T11-T12 disc space to the sacral terminus of the dural sac) in obese patients and individuals with abdominal compression from obesity or pregnancy (Deer 2009). Volume typically serves as a valuable diluent for intrathecal drugs, and resultant discrepancies can cause less dilution of the delivered agent(s) (Deer 2009). Bulk flow distributes CSF from the cerebral ventricular system to the cisterns at the base of the brain. A minority of the CSF leaves the cranial cavity and enters the vertebral subarachnoid space to pass downward posterior to the cord and then return upward anterior to the cord. The CSF bulk flow is affected by various factors including valsalva and arterial pulsations (4). The impact of normal CSF bulk flow on drug distribution from various locations of a catheter tip in the spinal canal is unknown. For instance, an anterior catheter may have more cephalad drug distribution whereas a posterior catheter may have more caudal distribution. In addition, with spinal pathology the CSF bulk flow may be disturbed affecting drug distribution. At this time, no firm recommendations can be made on optimum catheter tip location. However, if there is poor CSF return at the time of placement, consideration should be given to perform a radionucleotide study (Indium) to assess CSF distribution.

Previously described disparities in nerve root size and volume also impact response to intrathecal agents (Deer 2009). The panel recognizes the influence of a wide array of spinal and anatomical considerations on the patient selection process and encourages comprehensive review of physical attributes to ensure pre-implantation identification of potential technical challenges.

References

Factors Related to Patient Selection: Associated Medical Comorbidities
Patients with chronic pain often have coexisting medical conditions. The number and complexity of these comorbidities increase with age; the average octogenarian suffers from at least 4 concurrent medical problems (DiBari 2006, Rozzini 2002). These coexisting medical conditions influence the pain experience and overall outcomes associated with pain treatment (DiBari 2006). There are some well-recognized interactions between disease states and pain therapies, as well as less clear, but potential interactions that must be considered when selecting patients for treatment. In this section, we will consider some of the more common chronic illnesses and their established and/or potential influence on selecting patients for intrathecal drug therapy.

**Diabetes Mellitus.** In 2007, diabetes affected approximately 8% of the US population—23.6 million individuals—with an additional 57 million patients having blood glucose levels indicative of prediabetes (CDC, ADA). An estimated 60% to 70% of individuals experience some form of nervous system damage as a result of diabetes, with peripheral neuropathy being among the most severe complications in this patient population (NDIC). Risk factors for neuropathy include having had diabetes for more than 25 years, poor glucose control, hypertension, and obesity (NDIC). According to a survey of over 900 patients with diabetes, 60% of respondents indicated that they experienced chronic pain, many of whom reported difficulty in managing their medications, as well as an inability to engage in many activities of daily living (Krein 2004).

There is no evidence to help us better understand the role of intrathecal drug therapy in treating pain associated with diabetes or the relative risk of treating a diabetic patient with this modality, as compared to patients without diabetes. Nonetheless, it is clear that poor wound healing and an increased rate of surgical site infections do occur in this patient population. This is especially important as wound infection is the most common device-related complication associated with implanted intrathecal drug delivery systems (Follett 2004). There is also sound evidence that patients who undergo surgery with better long-term glycemic control—as evidenced by lower hemoglobin A1c levels immediately prior to surgery—have lower rates of surgical site infection. Thus, the panel recommends that diabetic patients, particularly those with poor glycemic control, be counseled regarding the increased risk of surgical site infection and that this elevated risk be carefully considered in the overall risk/benefit discussion. The escalated risk of wound infection in diabetics also warrants elevated vigilance for signs and symptoms of evolving wound infection after implantation. Although there are reports of successful resolution of surgical site infections in patients receiving intrathecal therapy using local incision and drainage, meticulous wound care, and systemic antibiotics aimed at the inciting organism, the majority of cases will require explantation of the device to effectively eradicate infection (Rathmell 2006).
Coagulopathies and Anticoagulant Therapy. Anticoagulant and antiplatelet therapy have become commonplace in the long-term management of many disorders, foremost among which is atherosclerotic coronary artery disease. Hospitalized patients frequently receive systemic treatment with heparin and heparin analogues; ambulatory patients often receive long-term therapy with warfarin or an increasing array of potent platelet inhibitors. Specific pain management concerns for anticoagulated patients influence perioperative anesthesia and analgesia-related safety decisions surrounding device implantation; as a result, regional anesthesia is typically avoided due to the risk of neurologic complications unless the patient is able to discontinue use of anticoagulants preoperatively (Horlocker 2003). Patients receiving anticoagulants are specifically at an increased risk for the development of spinal epidural hematoma during epidural catheter insertion or following catheter removal (Horlocker 2003, Chaney 2006). Despite an estimated incidence of 1:220,000 and 1:150,000 following intrathecal and epidural instrumentation, respectively, spinal hematomas were found to comprise almost half of the reported spinal cord injuries and were the primary source of malpractice claims in the American Society of Anesthesiologists Closed Claims database during the 1990s (Horlocker 2003, Chaney 2006). Anticoagulated and coagulopathic patients also have a potentially increased risk for tissue and vascular injuries as a result of the indwelling catheter used in placing and removing intrathecal devices (Horlocker 2003). Assessment of systemic factors and associated medications that might influence intraoperative coagulation is critical to minimize surgical complications (Knight 2007).

According to the Joint Commission, anticoagulants are 1 of the 5 leading classes of drugs that contribute to avoidable compromises in patient safety in the United States (Joint Commission). Following the introduction of low molecular weight heparin (LMWH), a series of reports of patients appeared who developed epidural hematomas and catastrophic neural injuries following neuraxial blockade (typically epidural anesthesia) (Horlocker 2003). This led the US Food and Drug Administration to add a black box warning to the drug label for LMWH, warning against the conduct of neuraxial anesthesia in patients receiving this agent (Horlocker 2003). Thereafter, the elevated risk of bleeding associated with a wide array of anticoagulant and antiplatelet agents has been systematically reviewed by the American Society of Regional Anesthesia and Pain Medicine (Table 1) (Horlocker 2003, Ghafoor 2007). When considering patients for initial placement of a trial intrathecal catheter or permanent implanted intrathecal drug delivery system, the panel recommends following these well-established guidelines.
Table 2. Recommendations for Neuraxial Anesthesia in Patients Receiving Thromboprophylaxis (Ghafoor 2007)\textsuperscript{13}

<table>
<thead>
<tr>
<th>Drug or Drug Class</th>
<th>Bleeding Risk</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfractionated heparin</td>
<td>No increased risk with neuraxial blockade; risk of heparin-induced thrombocytopenia with administration for (\geq 4) days</td>
<td>Subcutaneous heparin (5000 units every 12 hour) for DVT prophylaxis; remove indwelling neuraxial catheters 2-4 hours after last heparin dose</td>
</tr>
<tr>
<td>LMWHs</td>
<td>Moderate risk with single daily dose for DVT or PE treatment and thromboprophylaxis; high risk with combination of antiplatelet or oral anticoagulant medications</td>
<td>LMWHs should be held 24 hours before surgery and resumed 8-12 hours postoperatively; consider placement of an inferior vena cava filter before surgery for patients at high risk for PE; oral anticoagulants may be restarted 12 hours after surgery</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Spinal puncture and lumbar blockade contraindicated; high risk with combination of LMWH, heparin, or antiplatelet medications</td>
<td>Discontinue 4-5 days before surgery; INR must be (&lt;1.5) before surgery; warfarin 5 mg can be resumed immediately after surgery and adjusted to INR of 2.0-3.0</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>No significant increase in risk as monotherapy; high risk with combination of anticoagulant or antiplatelet medications</td>
<td>No specific recommendations; switch to COX-2 inhibitor for patients requiring anti-inflammatory therapy</td>
</tr>
<tr>
<td>Ticlopidine, clopidogrel</td>
<td>Risk based on history of easy bruising, excessive bleeding, female sex, and increased age; increased risk with combination of anticoagulant or antiplatelet medications</td>
<td>Discontinue ticlopidine 14 days before neuraxial blockade; discontinue clopidogrel 7 days before neuraxial blockade</td>
</tr>
<tr>
<td>Platelet glycoprotein IIb/IIIa antagonists</td>
<td>Contraindicated within 4 weeks of surgery; profound effect on platelet aggregation</td>
<td>Avoid neuraxial techniques until platelet function has recovered; neurologic monitoring after postoperative administration resumes</td>
</tr>
</tbody>
</table>

The risk of reinitiating chronic anticoagulant therapy following placement of a permanent intrathecal drug delivery system is unknown; only sporadic case reports suggest the safety of this practice. Nonetheless, the panel consensus is that the need for chronic anticoagulation is not an absolute contraindication to the use of intrathecal therapy.

*Immunocompromised Patients.* Studies have examined the safety and efficacy of intrathecal therapy in patients with advanced medical illness and significant compromise of their immune systems, including individuals with cancer and acquired immunodeficiency syndrome (AIDS). Outcomes of infectious diseases during opioid use are related to timing, dose, and route of analgesic administration (Risdahl 1998).\textsuperscript{14} Based on indirect comparative data, reported device infection rates are similar between immunocompromised patient populations (eg, those with cancer or AIDS) and all-treated individuals (Follett 2004, Staats 2003, Smith TJ 2002).\textsuperscript{7,15,16} Although it is uncertain at present whether immune compromise independently increases the rate of intrathecal therapy failure due to device infection, logic suggests that a compromised immune system may elevate the risk of infection. In the absence of conclusive data, the panel...
recommends careful evaluation of potential risks and benefits when considering intrathecal therapy for patients manifesting with significant immune compromise.

**Chronic Infection.** The presence of active infection is typically viewed as a contraindication to placement of all implantable devices. Any type of active infection may introduce the risk of bacteremia and seeding of the implanted system, although the actual magnitude is unknown. Patients previously identified as carriers of methicillin resistant *Staphylococcus aureus* (MRSA) are known to be at an increased risk for infection. A preoperative nasal swab should be incorporated into the selection process for these patients to confirm that MRSA is not present at the time of surgery (Knight 2007). Particularly for those patients with noncancer pain, the panel views the presence of any active infection as a relatively strong, although not absolute, contraindication to placement of a permanent intrathecal drug delivery system. Complicated cases may benefit from consultation with an infectious disease specialist to provide further insight into condition-specific safety concerns (Stearns 2005).

**Obesity-Related Obstructive Sleep Apnea.** The prevalence of obesity has reached epidemic proportions, affecting between 33% and 35% of US adult men and women, respectively, from 2005 to 2006 (Ogden 2007). Obesity predisposes individuals to developing symptoms of obstructive sleep apnea (OSA) due to profound anatomical changes that produce upper-airway obstruction during normal sleep, causing temporary apneic episodes. Present in more than 18 million US adults (NSF), OSA can lead to significant sequelae, including chronic carbon dioxide retention and pulmonary hypertension. OSA has also been associated with an increased sensitivity to the respiratory-depressant effects of opioids; thus, use of intrathecal opioids may carry an elevated risk of respiratory depression in this patient population (Farney 2003).

Although the long-term effect of intrathecal therapy in patients with OSA is unknown, the use of chronic oral opioids in OSA patients has been identified as a significant risk factor associated with adverse outcomes. Three case reports described by Farney et al illustrate distinct complications of long-term, sustained-release opioids on respiration compared with common respiratory abnormalities exhibited by opioid-naïve OSA patients (Farney 2003). Opioid use was associated with increased apnea duration and hypoxia severity during non-rapid eye movement sleep (NREM), ataxia with irregular respiratory pauses during NREM sleep, and severe hypoxemia (Farney 2003). Further investigation is needed to explore the extent to which long-term intrathecal opioid therapy may interact with OSA (Farney 2003).

The American Society of Anesthesiologists recently published updated recommendations to guide the conduct of clinicians in administering neuraxial opioids to potentially high-risk patients (Horlocker 2009). Although these guidelines are intended for the management of acute pain, the recommendations may be relevant in the chronic pain setting as well. Horlocker et al advise physicians to obtain a detailed history and perform a physical examination—which should include, but is not limited to, the recording of baseline vital signs, airway, heart, lung, and cognitive function—as part of the patient selection process (Horlocker 2009). The panel concluded that continuous intrathecal opioid administration is acceptable in patients with OSA, provided there is adequate monitoring throughout the administration period to minimize the risk of adverse effects (Table 3) (Horlocker 2009). Therefore, it is permissible for OSA patients to be implanted with a drug delivery device as long as they are carefully evaluated for potential respiratory complications and meet all other criteria for patient selection.
Table 3. Recommendations for Early Detection of Respiratory Depression following Opioid Administration (Horlocker 2009)\textsuperscript{21}

- Patients should be monitored for adequacy of ventilation, oxygenation, and level of consciousness.
- Monitoring should take place at least once per hour during the first 12 hours following opioid administration; thereafter, monitoring should occur at minimum once every 2 hours for 12 hours.
- 24 hours after administration, monitoring should occur every 4 hours for at least 48 hours.
- Increased monitoring is warranted for high-risk patients (eg, those with obesity and/or sleep apnea).

**Chronic Lung Disease.** Chronic lung disease manifests in a variety of forms, frequently presenting as reactive airway disease, restrictive pulmonary disease, and chronic obstructive pulmonary disease (COPD). Chronic lung disease currently affects more than 35 million individuals in the United States and causes more than 400,000 US deaths annually (ALA).\textsuperscript{22} Of these chronic lung diseases, COPD patients typically experience significant retention of carbon dioxide and are more prone to respiratory depression and respiratory arrest with the administration of systemic opioids than the general population. A retrospective case-controlled analysis by Taylor et al found that patients with COPD are most at risk for a respiratory event when administered opioids following surgery (OR 5.09; 95\% CI) (Taylor 2005),\textsuperscript{23} as compared with patients without chronic lung disease. Due to their known respiratory depressant effects and potential to worsen hypercapnia, the 2001 Global Initiative for Chronic Obstructive Lung Disease guidelines indicates that narcotics are contraindicated for patients with COPD (Pauwells 2002).\textsuperscript{24}

Extrapolating to the use of intrathecal opioids, it is reasonable to presume that COPD patients will also have a greater tendency toward respiratory depression when administered opioids via an implantable device. Thus, the panel recommends close monitoring in patients with chronic lung disease during any intrathecal trial and immediate post-implantation of a permanent system, particularly within the 24 hours following surgery. Evidence has shown that most respiratory events secondary to opioid administration occur within 24 hours post-surgery; more than half occur within less than 12 hours (Taylor 2005).\textsuperscript{23} Recommendations provided by the American Society of Anesthesiologists may also be of assistance in treating this patient population (Table 3) (Horlocker 2009).\textsuperscript{21} However, long-term risk of intrathecal therapy in chronic lung disease patients is unknown.

**Cardiac Disease.** Limited data support the notion that cardiac abnormalities may independently alter the risk of intrathecal therapy when the N-type calcium channel antagonist ziconotide is used, and the potential for dose-related cardiovascular adverse events may also exist. In a randomized controlled safety and efficacy study of intrathecal ziconotide, investigators noted that cardiovascular adverse effects—namely postural hypotension and hypotension—occurred more frequently in patients in the active treatment group, as compared to those in the placebo cohort (33.3\% vs 10\%, respectively) (Staats 2004).\textsuperscript{15} Notably, 32.3\% of postural hypotension events occurred at doses greater than 0.1 \(\mu\)g/h versus 17.1\% transpiring at doses less than or equal to 0.1 \(\mu\)g/h (Staats 2004).\textsuperscript{15} The researchers concluded that in addition to initiating treatment at lower dosages, using smaller dose increments and increasing the time between dose titrations reduced the frequency of adverse effect (Staats 2004).\textsuperscript{15} Although evidence suggests that ziconotide leads to cardiac conduction abnormalities when administered systemically, there
is little support in the literature to confirm that the typical doses used intrathecally in clinical practice have any impact on the cardiac conduction system.

Since there are no specific guidelines detailing the impact of cardiac abnormalities on intrathecal therapy, the panel recommends that all candidates for intrathecal device implantation with a history of cardiovascular disease be evaluated via the risk stratification guidelines outlined by the American College of Cardiology/American Heart Association (ACC/AHA Task Force 2007). Similarly, the possibility of perioperative morbidity or mortality should also be assessed for patients 50 years of age or older, due to the prevalence of cardiac risk factors in this population (ACC/AHA Task Force 2007). An evaluation that reveals 1 or more major clinical risk factors (ie, unstable coronary syndromes, decompressed heart failure, significant arrhythmias, or severe valvular disease) may require that surgery be postponed or cancelled to allow for proper management of the condition. Although it is permissible to proceed with implantation in patients with a history of ischemic heart disease, compensated or prior heart failure, or cerebrovascular disease, extreme caution should be exercised when operating on individuals with these intermediate-level risk factors (ACC/AHA Task Force 2007).

**Kidney Disease.** Approximately 12% of US adults, or 23 million individuals, suffer from chronic kidney disease (CKD), with over half a million adults being treated for end-stage renal disease (NIDDK). There is little available data, but the presence of CKD—including end-stage renal disease requiring hemodialysis—does not appear to impact the efficacy or safety of intrathecal therapy. However, patients with CKD have a higher incidence of cardiac disease compared with the general population. It is, therefore, recommended that clinicians consider the risk-benefit ratio outlined by the ACA/AHA prior to proceeding with device implantation. Patients with a preoperative creatinine level greater than 2 mg/dL are at an increased cardiac risk after surgery and require escalated surveillance before the decision to proceed with intrathecal delivery can be made (ACA/AHA Task Force 2007). For CKD patients deemed appropriate for surgery, clinicians should also be aware of challenges associated with finding a comfortable location for the placement of an indwelling pump in individuals receiving peritoneal dialysis.

**Panel Recommendations.** Intrathecal therapy offers therapeutic advantages to patients with a variety of painful disorders and advanced medical illnesses that affect a wide range of organ systems. The panel does not recognize any pre-existing medical comorbidity as an absolute contraindication for intrathecal drug therapy. When evidence from the established literature is not available to guide the patient selection process, clinicians should abide by published guidelines and practice recommendations for the existing comorbidity and use clinical judgment to ascertain the appropriateness of proceeding with device implantation.

**REFERENCES**


Prior Therapy and Its Results

Pain management strategies are individually tailored based on comprehensive evaluation of overall health status and pain-related history (ASA 1997). Accurate diagnosis and appropriate therapeutic management are essential to optimize pain relief and quality of life (ASA 1997). A step-wise approach is typically employed and tailored to the individual patient’s needs and guided by the best available evidence. In general, after initiating careful diagnostic evaluation, pain treatment is begun using the most conservative approach. Efforts are aimed toward amelioration of the underlying disorder causing the ongoing pain. Based on the problem at hand, treatment may begin with pharmacologic therapy with or without concomitant physical therapy. In many cases, direct intervention with image-guided pain treatment can be beneficial in speeding the resolution of acute painful exacerbations. In those with persistent pain, more aggressive strategies are often adopted after failure is realized with less aggressive treatment. A pain treatment continuum for chronic noncancer pain begins with conservative options, such as exercise programs, meditation and relaxation techniques, and over-the-counter pain medications (Deer 1999, Krames 1997). Subsequent steps include adjuvant medications for treating neuropathic pain, physical rehabilitation, somatic and sympathetic neural blockade for specific pain conditions, cognitive and behavioral therapies, and/or oral or other systemic opioid medications (Deer 1999, Krames 1997). More aggressive options are reserved for the small fraction of patients who do not improve with more conservative measures and include spinal cord stimulation, spinal (intrathecal) drug delivery, and neurodestructive procedures (Deer 1999, Krames 1997). Patient selection criteria for intrathecal drug delivery system implantation—namely exhaustion of all attempts at treatment of the underlying disorder responsible for the ongoing pain, failure of less invasive therapies, and inadequate effect or intolerable side effects with use of oral opioids—reflect this step-wise therapeutic approach (Deer 1999). Intrathecal drug delivery in noncancer-related pain has not been subject to controlled trials, but numerous observational studies suggest that it provides significant pain reduction in certain patients whose chronic pain fails to respond to more conservative management (Prager 2002, Turner 2007).
Opioids can provide effective analgesia via many routes of administration—oral, transdermal, and intravenous or neuraxial routes (epidural and intrathecal)—and the simplest effective route should be used for each patient. Chronic opioid therapy in the long-term management of noncancer-related pain remains controversial (Furlan 2006, Morley-Forster 2003, Kalso 2004). Advocates point to long-term efficacy and improvement in function in patients with chronic painful conditions, including low back pain, whereas opponents cite difficulties in prescribing these drugs over extended periods of time [B] When treating a patient with long-term opioids, many drugs are available. The traditional paradigm for opioid treatment is based on cancer pain management (Ballantyne 2003). In this approach, patients with significant chronic pain are given a long-acting opioid for continuous analgesia; short-acting opioids may cause fluctuations in pain control. A small dose of a short-acting drug is also available for intermittent pain that occurs with activity and “breaks through” the control provided by the long-acting drug alone. The focus of cancer pain management is on both time (long acting) and pain (breakthrough) contingent medication whereas the focus of non-cancer pain management is more on time contingent and less on pain contingent medications.

Nearly every available opioid has been used successfully in treating chronic low back pain, including short-acting agents (eg, hydrocodone, oxycodone), alone or in combination with ibuprofen or acetaminophen, and long-acting agents (eg, methadone, transdermal fentanyl, controlled-release oxycodone). Oral or transdermal opioids are the most common agents used, and an estimated 80% to 90% of patients with chronic noncancer pain attain adequate pain control with these conservative therapies (Krames 1997, Belverud 2008). However, there remains a small but significant percentage of chronic pain patients who do not achieve effective pain relief with traditional regimens. Even those who initially respond to opioid therapy may eventually require alternative treatments to maintain analgesia. The relief provided by opioids for some patients may be temporary; systemic administration is associated with a high likelihood of drug tolerance due to pharmacokinetic variation (eg, increased drug clearance) or pharmacodynamic adaptations (eg, reduced responsiveness of opioid receptors), necessitating an escalation of dose amount and/or frequency (Sinatra 2006). A prospective study of 60 patients receiving oral morphine for noncancer pain found that 43% of responders required a dose increase during the 241-day observation period (Schulzeck 1993). Factors such as type of pain, adjuvant opioid use, the presence of comorbidities, and psychosocial issues are thought to increase dosing frequency (Sinatra 2006).

Intolerable adverse effects—another common drawback of systemic opioids—are more likely to occur at higher dosages, and therefore, can be problematic for patients requiring dose escalation to achieve adequate pain control. Commonly reported adverse effects include gastrointestinal distress (eg, nausea, vomiting, constipation, diarrhea) (Willis 1999); impaired cognition (eg, memory lapses, confusion) (Willis 1999); urinary retention or incontinence (Willis 1999); pruritus (Sinatra 2006); interference with the touch sensation (Deer 1999); impaired motor function and sympathetic reflexes (Deer 1999); and central nervous system conditions, such as drowsiness or cloudiness (Deer 1999). Clinical experience suggests that higher opioid doses may produce a greater-than-normal sensitivity to pain, possibly as a result of increased stimulation of the central nervous system that does not occur with lower opioid dosages (Sinatra 2006).
There are no studies that directly address the correlation between response to systemic opioids and subsequent response to intrathecal therapy for the management of noncancer pain. Clinical experience and extrapolation from the extensive experience with treatment of cancer pain suggests successful pain relief can be achieved in patients with a previous history of poor pain relief or adverse reactions with systemic opioids (It looks like the literature support for this is summarized below). Greater efficacy with intrathecal therapy as compared with systemic treatment may stem from the direct application of agents close to their site of action at the spinal dorsal horn. Intrathecal administration also allows for a variety of medications to be administered as monotherapy or in various admixtures; if morphine is ineffective or has intolerable adverse effects, the physician may attempt a course of another opioid (eg, hydromorphone, fentanyl, or sufentanil) or a “cocktail” combining agents from different drug classes (eg, an opioid plus bupivacaine) (Deer 2007).

A number of uncontrolled studies have found that intrathecal therapy can be successful in patients with moderate-to-severe pain who have failed systemic analgesic therapy (Smith 2008). Hassenbusch et al conducted a prospective observational study of 18 patients with neuropathic noncancer pain who were refractory to systemic therapy and found that 61% (11 patients) had good or fair pain relief, with an average pain score reduction of 39% (Hassenbusch 1991). In a prospective observational study of 30 patients with neuropathic noncancer pain who were refractory to systemic treatment, Anderson et al found that 50% of participants reported at least a 25% reduction in pain at 24 months post pump implantation (Anderson 1999). Similar results where reported by Kumar et al in a prospective analysis of 16 patients who were refractory to conservative drug therapy with regular consumption of narcotic analgesics and, in some cases, spinal cord or deep brain stimulation. Patients included in this study achieved more than a 50% reduction in pain following a trial of IT morphine. After device implantation, the average pain reduction at 6 months was 67.5% and 57.5% at last follow-up point (mean 29.14 months); the researchers determined that 75% of patients reported treatment “successes” with intrathecal therapy (Kumar 2001). Notably, these studies did not differentiate between patients who failed systemic therapy due to nonresponsiveness and those who failed due to intolerability.

Patients who achieve adequate pain control with systemic opioids, but discontinue therapy due to intolerable adverse effects are likely to respond more favorably to intrathecal opioids than those who reported inadequate pain relief despite use of high dose systemic opioids. Conversely, there is no evidence to confirm that patients who have not achieved an analgesic effect after a reasonable trial of several systemic opioids at adequate doses will achieve better/worse outcomes with intrathecal therapy (Krames 1997).

Panel Recommendation. For patients with chronic noncancer pain, a step-wise approach to therapy in which treatment begins with the least aggressive approach and progresses only when therapy fails to provide adequate analgesia is recommended. Intrathecal therapy should be considered only when more conservative treatment options have failed. A direct correlation between response to systemic opioids and subsequent response to intrathecal therapy has not been clearly established; nonetheless, uncontrolled trials and clinical experience suggest that patients who achieve a 50% or greater reduction in pain with systemic opioids are likely to achieve a therapeutic benefit with intrathecal therapy (Krames 1997), accompanied by a lower rate of adverse effects. However, patients who report no pain reduction when treated with systemic opioids may not achieve as sufficient analgesia with intrathecal drug delivery. The spinal dorsal horn is rich in receptors and ion channels that modulate pain. It is reasonable to
assume that combination spinal drug delivery is likely more effective than systemic therapy; however, there is no literature to support this. In addition, there is no literature to support the predictive value of response to systemic non-opioids when administered spinally.

References:
Diagnosis and Pain Characteristics

Diagnostic assessment of the patient with chronic noncancer pain should encompass a complete physical, neurologic, radiologic, psychological, and social evaluation (Deer 1999, Ghafoor 2007). A detailed pain history and a review of the patient’s medical records, prior pharmacologic treatments, and laboratory findings should be incorporated into the evaluation (Deer 1999). During the initial stages of this process, the decision to use an implanted intrathecal drug delivery system considers pain diagnosis, pain characteristics (type and intensity), and impact on the patient’s functionality and quality of life.

Preliminary assessment for intrathecal therapy relies on the ability of the clinician to accurately diagnose the cause of the patient’s pain, with a view toward identifying an observable pathology consistent with chronic pain (Deer 1999, Krames 1996). Common disease states and diagnoses for which intrathecal drug delivery is indicated include neuropathic syndromes (eg, thalamic syndrome, spinal cord injury, diabetic neuropathy, or reflex sympathetic dystrophy); radicular pain from failed back surgery syndrome; complex regional pain syndrome; osteoporosis; pancreatitis; postherpetic neuralgia; phantom limb pain syndrome; compression fractures; and other disorders caused by injury or irritation to the nervous system (Deer 1999, Ghafoor 2007). Unlike pain associated with terminal illness, noncancer pain patients tend to have longer life spans and require extended therapy that can range from months to years based (Deer 1999).

The type of pain a patient reports—typically classified as visceral/somatic nociceptive, neuropathic, or mixed neuropathic nociceptive pain—may greatly impact therapeutic outcomes, as response to intrathecal delivery can vary depending on the pain presentation (Deer 1999). However, there is conflicting evidence as to which pain type is best suited to treatment with an implantable device (Deer 1999). Patients with visceral nociceptive pain (ie, pain that is diffuse and characterized by a constant, dull ache or a pressured feeling) or somatic nociceptive pain (ie, pain that is well-localized, constant aching, or throbbing) often respond well to intrathecal therapy (Deer 1999). Patients with nociceptive pain may achieve a greater therapeutic effect than those with neuropathic (ie, burning, shooting, tearing, electric-like pain) or mixed nociceptive/neuropathic pain. For example, a multicenter, retrospective study of 429 patients receiving intrathecal therapy found that patients with nociceptive pain tended to experience greater relief than those with neuropathic or mixed pain (Paice 1996). Yet, other research suggests that neuropathic pain may in fact be responsive to intrathecal therapy. Most notably, a retrospective observational study of 120 patients with chronic noncancer pain syndromes found that long-term intrathecal therapy reduced neuropathic pain by an average of 62% (Winkelmuller 1996). Although the researchers reported that patients with nociceptive pain had the best initial response to treatment—with an average pain reduction of 77% after 6 months—their level of relief decreased to 48% by last follow up (Winkelmuller 1996). Patients with mixed nociceptive/neuropathic pain are typically the most difficult to treat successfully, often necessitating the use of combination therapy to achieve effective analgesia (Deer 1999, Deer 2004).

Pain intensity should also be assessed as part of the diagnostic evaluation (Deer 1999). Numerous tools—including numerical pain rating scales; visual analog scales; verbal rating scale; faces pain-rating scales; and pain questionnaires—are available to assist clinicians in assessing and quantifying pain intensity (Deer 1999, Sinatra 2006). An accurate measure of
pain intensity is important not only during the patient selection process, but throughout treatment since it serves as a baseline calculation from which to determine the effect of therapy. In fact, the majority of research studies involving intrathecal therapy include pain severity as an inclusion criterion to provide a basis for evaluating efficacy across trial participants. Pain intensity also has an important impact on treatment outcomes; although patients with greater pain severity may achieve a reduction in pain level via intrathecal drug delivery, their overall pain severity may still remain high compared with individuals who present with a lesser magnitude of initial pain (Thimineur 2004).

A final consideration during the diagnostic evaluation takes into account the substantial impact chronic pain has on functional ability and quality of life. Only patients who demonstrate severe limitations as a result of chronic pain—those manifesting with psychological disturbances (including depression, anxiety and stress), poor appetite and weight loss, decreases in physical and recreational activities, sleep disturbances, or a change in interpersonal relationships and economic stability—should be considered for intrathecal therapy (Deer 1999). Successful treatment outcomes may afford the patient the opportunity to return to activities of daily living, thus improving quality of life.

Panel recommendation. Diagnosing the cause of pain is critical to ensuring proper patient selection. Patients with nociceptive pain are ideal candidates for intrathecal therapy, although research suggests that therapy can also be effective for patients with neuropathic and mixed nociceptive/neuropathic pain. Given the risks associated with implanted intrathecal drug delivery systems, pain intensity and its impact on functionality and quality of life should also be considered throughout the evaluation process.

References:
Factors Related to Patient Selection

Technical Factors: Device-Related Limitations. There are a number of technical concerns that must be considered when selecting a patient for treatment using intrathecal drug therapy. Most notable is the size of the intrathecal pump and the subcutaneous position and route that the tunneled catheter will take during surgical placement. Before the procedure, the patient must clearly understand the size and location of the pocket for the intrathecal pump. Most devices are large, and the only region suitable for placement is the left- or right-lower quadrant of the abdomen (Knight 2007). However, in patients with an overhanging panniculus, higher placement may be necessary. It is important to mark the pump location while the patient is in the sitting position for optimum location. Special care must be taken to avoid proximity to the anterior rib or iliac crest, which can cause painful contact of the pump with these structures, even after complete healing of the surgical incisions. Placement can be complicated by extensive scarring caused by prior abdominal surgery. The presence of a colostomy of other enterocutaneous ostomy must be carefully considered when selecting the position for creation of the pump pocket. The presence of ongoing infection or significant skin breakdown anywhere along the course of the proposed position for the tunneled catheter is a relatively strong contraindication to placement. Minor variations in the depth of the implant site are appropriate based on weight ranges, with special consideration to maintain pump accessibility for required refills (Knight); the pump may be implanted within the mid-fat plane of the lower quadrant of the abdomen or directly over the anterior fascia of the rectus abdominis muscle to accommodate for variation in body habitus of individual patients (Knight 2007). It is necessary to secure the pump with suture to prevent rotation. Fascia is the optimum tissue for securing the pump but if the pump is placed in the mid-fat plane, the pump can be sutured to the fat as scar tissue will form rapidly around the sutures and pump securing the pump in place.

Postoperative and long-term patient management require direct access to personnel with the expertise to troubleshoot and maintain the implanted device. The implanting physician must be certain that the patient will have adequate access to follow up before proceeding with placement of the device. Access to a qualified expert at a facility with appropriate clinical infrastructure for postimplantation device refills, dosage adjustments, and reprogramming is essential to the safe and effective maintenance of intrathecal therapy (Krames 1997; Krakovsky 2007). The treating physician must be familiar with opioid and intrathecal therapies, including methods to clinically manage device-related adverse effects (Krames 1997) such as postoperative infection. Patients with limited transportation or those living in remote regions may not be reasonable candidates for intrathecal therapy based solely on limited access to the needed follow-up.

The use of intrathecal drug therapy is technically challenging and relies on an understanding of the pharmacology of intrathecal opioids and proper use of the infusion device. The role of the individual practitioner is critical in assuring safe use of intrathecal opioid therapy. A recent large-scale epidemiology study has established that there is excess mortality associated with the use of intrathecal opioid therapy for the treatment of noncancer pain (Coffey RJ 2009). Every practitioner using intrathecal therapy must understand that there is risk of fatality, particularly
soon after implantation. In the absence of data to guide practice, we must adopt a common sense approach. It seems logical that practitioners can minimize their contribution to this risk by 1) initiating intrathecal therapy with the lowest dose that can be reasonably predicted to provide efficacy; 2) avoiding use of concomitant central nervous system depressants in the immediate post-implantation period; 3) gaining an expert understanding of the intrathecal drug pump, its construction, and proper programming; 4) personally overseeing all aspects of the initial programming; 5) avoiding use of excessively concentrated solutions during initiation of therapy to minimize the delay in onset of drug effects associated with slow infusion rates; and 6) routinely calculating when new drug will first enter the intrathecal space and warning the patient and their caregivers to be most vigilant during this interval of time (Rathmell JP 2009).

Regulatory barriers related to opioid use may impede optimal treatment for patients with noncancer pain (Krames 1997). Although federal law permits opioid use for intractable chronic pain, variation exists in state laws (Joranson 1993). Legislation and oversight at the state level in some instances has imposed restrictions on the initiation and maintenance of chronic opioid therapy, particularly for patients with noncancer pain (Joranson 1993). State-enacted legislation has historically concentrated on conventional routes of opioid administration, nonetheless intrathecal opioid therapy certainly extends the relevance of any regulatory restrictions. Indeed, there are notable case reports of abuse and diversion that involve the removal of concentrated drug solution from an implanted intrathecal drug delivery device (Gock 1999, Burton AW 1998). Intrathecal drug delivery devices gain approval for specific agents, thus legislation affecting opioids imposes limitations on the use of opioid-compatible pumps. Widespread off-label use of intrathecal opioid agents for pain management can further exacerbate regulatory constraints (AAPM 2009).

(Should we comment on selecting a constant flow rate versus programmable pump? I am not using constant flow rate pumps but patients with stable infusion rates requiring a pump replacement may be suitable for a constant flow rate.)

References:

Associated Psychological Considerations
Psychological factors intermingle with physical characteristics to influence the experience of pain through behavioral/environmental, cognitive/affective, and neurochemical/physiological mechanisms. This interplay of multidisciplinary issues supports the relevance of a tailored psychological assessment as part of the patient selection process for intrathecal therapy (IT). Although insurance companies vary as to their requirements for psychological screening prior to preimplantation drug trials or internalization of the device, it has become common practice to obtain a detailed report of the patient’s psychological makeup and its implications for successful participation in long term IT.

A psychological consult in the pain management setting entails the identification of relevant psychological factors and their potential impact on long term outcomes. Areas of concern may include the patient’s ability (a) to be educated as to expectations for, and benefit of, the treatment modality; (b) to prepare for, commit to, and subjectively assess long term therapeutic impact; and (c) to participate in, and gain benefit from, concomitant behavioral or cognitive therapy designed to improve functional activities and maximize quality of life (Doleys 2002). Attention to potentially modifiable psychological states, such as depression and anxiety, that can exacerbate the experience of pain and impair the ability of the patient to cope effectively is essential. Importantly, the role and impact of the psychosocial factors is often dynamic and can fluctuate in relationship to time and clinical or personal circumstances. For example, the placebo effect and the development of pharmacologic side effects (ie, hyperalgesia, tolerance) can contribute to poor outcomes despite pain relief during a trial and should be addressed promptly. Changes in mood and psychosocial status—including depression, divorce, and interpersonal conflicts—can also emerge as unanticipated psychosocial complications (Doleys 2003).

Furthermore, restoring independence and engagement in certain physical activities, such as work or household chores, as a result of improved pain control, might prove less reinforcing to the patient than originally presumed. For these reasons, parallel strategies for addressing psychological issues and adverse clinical responses to IT should be developed and form the foundation for tailoring long-term therapeutic algorithms.

Psychological Variables as Predictors of Outcomes. Psychological conditions—such as suicidal depression, schizophrenia with active psychotic behavior, and active drug abuse—are routinely associated with unfavorable outcomes for implantable pain therapies (Nelson 1996). In a systematic review of the literature relating to pretreatment psychological variables as predictors of outcome, Celestin et al identified a positive relationship between one or more psychological factors and poor treatment outcomes in 92% of the 25 studies they reviewed (Celestin 2009). Presurgical somatization, depression, anxiety, and poor coping tended to be predictive of a poor response to treatment. Although these data suggest a possible correlation between psychological status and the effect of pain-related treatment, current empiric research has yet to reveal a specific set of variables associated with positive or negative outcomes. This, in part, may be due to variability in the mythological quality of the research. Additionally, the role of psychosocial factors in “predicting” successful outcomes with IT can be obscured by vast number of potential psychosocial variables, types and locations of pain, and medical comorbidities, as well as by the patient’s psychological status and life circumstances.
Psychological variables represent only relative—rather than absolute—contraindications. As such, the appropriateness of a candidate for implantation cannot be determined or predicted by a single test or clinical interview. For example, contrary to what might be expected, a study by Doleys and Brown demonstrated that patients with mildly abnormal Minnesota Multiphasic Personality Inventory-2 (MMPI)-personality-profiles reported a higher percentage of improvement in pain after four years of IT compared with patients with a more “normal” MMPI (Doleys 2001). Thus, patients should not be excluded based solely on such findings without first considering other aspects of the psychological evaluation. Furthermore, presuming the existence of “predictors” of outcome assumes a standard set of outcomes or goals for all patients, when in fact, the goals are likely to vary for cancer versus noncancer pain and for pain versus spasticity. Likewise, the treatment approach may vary based on the specific condition (eg, severe complex regional pain syndrome-type I or II versus failed back surgery syndrome or multilevel degenerative disc disease). The outcome goal(s) for a 38-year old male with a mild radiculopathy following modified microdiscectomy, who is in good health, has 15 years of formal education, and aspirations of returning to work may be quite different than those for an 78-year old female with multiple level compression fractures. The identification of a fixed set of psychosocial predictors is most likely to occur when examining a highly constrained and homogenous group of patients (Howell 1997). To date, it also appears more likely that one will identify characteristics associated with “poor outcomes” than with “good outcomes (Celestin 2009, Doleys 1997).”

Although a detailed psychological assessment may have limited prognostic value, the evaluation process can be used to facilitate the initiation of appropriate individualized treatment to properly prepare the patient for implantation and long-term treatment (Doleys 2002). Targeted psychological/behavioral interventions can often mitigate the impact of aberrant psychological issues (ie, excessive reinforcement for maladaptive pain behaviors) and create a patient with a more favorable prognosis. The use of the psychological assessment as a means of addressing potentially modifiable problems during the patient selection process may enhance the applicability of IT technology and prevent an over emphasis on the development of absolute exclusionary criteria (Doleys 2003).

**Strategies for the Psychological Evaluation.** With an estimated 75% of chronic pain patients identified as having relevant psychological factors (Doleys 1997), a focused pretrial psychological consult is often beneficial. The primary goal of assessment—which usually includes a one-hour clinical interview—is to develop a functional patient description that offers context for the pain behavior. Communication should transpire between the healthcare team, patient, and support person. At least two studies have documented that significant others tend to perceive outcomes of IT differently than patients (Doleys 1998, Willis 1999), and incorporating others involved with the patient’s care into the assessment can offer an alternative perspective from which to consider the patient-provided information. Dialogue with the patient can reveal “pain modifying” events, which may exacerbate or reduce pain severity. Behavioral observations and functionally oriented questions may uncover behavioral tendencies—such as activity avoidance, anticipatory pain, and other maladaptive responses—which define the scope of the pain impact. Information obtained through the clinical interview, psychological test/questionnaire, a review of records, behavioral observations, and consultation with other healthcare providers and significant others can provide valuable insights as to the patient’s perception of their condition, general coping strategies, expectations of therapy, overall psychological status, and their “readiness for change.” In this regard, clarification of a patient’s
goals and priorities, as well as expectations, is fundamental. The more vague or ambiguous the patient is, the greater the need to identify appropriate and measurable functional goals and consider a functionally-oriented trial (Doleys 2007, Follett 2004).\textsuperscript{12,13}

A variety of psychological tests, questionnaires, and instruments are available for use during the evaluation. Preference should be given to scale-based instruments whose validity and reliability are supported by suitable research and those that provide a mechanism for assessing dissimulation, malingering, or symptom exaggeration/magnification (see Doleys and Doherty, 2000, for a more detailed discussion) (Doleys 2000).\textsuperscript{14} In addition, the evaluation of the pain patient should incorporate a number of dimensions, including pain intensity (eg, McGill Pain Questionnaire, visual analogue scale); mood, personality, and overall psychological functioning (eg, MMPI, Symptom Checklist 90-R, State Trait Anxiety Inventory); pain beliefs, coping, and acceptance (eg, Multidimensional Pain Inventory, Chronic Illness Problem Inventory, Coping Strategies Questionnaire, Chronic Pain Acceptance Questionnaire); level of functioning (eg, Oswestry Disability Questionnaire, Sickness Index Profile); and cognitive functioning (eg, Mini Mental Status Exam). Schocket et al describe a protocol that encompasses a number of different tests and questionnaires utilizing a point system to account for the presence of certain risk factors and tests scores (Schocket 2008).\textsuperscript{15} Patients are grouped according to their cumulative points as (a) acceptable to proceed, (b) will require postsurgical psychological intervention, (c) requires presurgical psychological intervention, (d) noninvasive therapy recommended, or (e) recommend no treatment. When preparing for an evaluation, consideration of the sensitivity and specificity of the tests selected, as well as the related expense and patient time needed for completion is also required. Once a test has been administered, its interpretation and meaning should be done in the context of information gathered through a clinical interview.

According to Williams and Epstein psychological factors most routinely assessed during an consult consist of psychiatric disorders, such as axis II or personality disorders; depression; substance abuse; secondary gain, including litigation and worker’s compensation; and motivation for receiving an implantable device (Williams 2002).\textsuperscript{16} Issues of cognitive functioning gain relevance as those who are cognitively impaired (eg, through dementia, traumatic brain injury, Alzheimer’s disease) may have difficulty identifying and communicating changes in pain and may respond in a different manner to IT than patients who are not cognitively impaired (Doleys 1997).\textsuperscript{9} Additional challenges associated with cognitive dysfunction, including difficulty with comprehending goals, expectations, and rationale for IT, might require supplementary education or closer involvement of a support person. Other areas to explore during the evaluation include any untreated or undertreated major affective disorder or alcohol/drug problems, patient expectations of pain and intended therapy, and type and degree of social support (Doleys 2004).\textsuperscript{17} To facilitate the process, it might be of benefit to the patient’s physician to create a letter requesting an evaluation of areas of interest/concern as an introduction to seeking the psychological consultation, rather than asking for “clearance”—an extremely vague term that can be influenced by available clinical resources, the evaluator’s experience and attitudes toward IT, relationship with the physician, and/or economic concerns.

\textit{Related Influences on the Psychological Assessment.} Patient beliefs and coping strategies may shape positive or negative therapeutic outcomes by revealing the level of vulnerability to external influences on pain management. Viewpoints related to more favorable results include (a) patient understanding of pain as a multifactorial experience that can be affected by the patient’s own attitudes and behaviors, (b) belief in the effectiveness of exercising coping skills
and acceptance, and (c) active involvement in treatment-related decisions (4). In contrast, individuals who tend to restrict the pain experience to its physical characteristics or medical cause and minimize the role of psychosocial factors are more likely to experience negative outcomes. Coping strategies can be divided into control-based, such cognitive coping, or acceptance-based methods. Several studies have demonstrated that acceptance-based strategies have fared better than control-based methods in experimental and controlled clinical situations with regard to increasing pain threshold, pain tolerance, and associated functioning and may have some advantage over control-based strategies (Gutierrez 2004, Hayes 1999, McCracken 2003).

Perhaps one of the most systematic approaches to a preimplant trial is to view it as a single-subject (ie, “N-of-1”) clinical study. Individualized goals are developed in cooperation with the patient when using this method, which allows the effect of one or more treatments, pharmacological agents, or dosages on the patient’s ability to achieve the goals to be compared. This model was exemplified by Cepeda et al in a case study that focused on a patient undergoing a preimplant trial of spinal cord stimulation (SCS) (Cepeda 2008).21 The investigators systematically compared the effects of SCS to transcutaneous electrical nerve stimulation (TENS) across a five-day period. In this instance, the two treatments produced similar results; therefore, the device was not implanted. By thoroughly evaluating patient response in varying clinical scenarios, this approach may prevent “false-positive” outcomes (ie, a positive trial followed by a poor long-term outcome).

Despite the value of measurable psychological characteristics, clinical scenarios can exist in which the severity of physiologic symptoms may take precedence over psychological concerns. The demands of certain conditions—such as a patient with complex regional pain syndrome manifesting a very dystrophic, swollen, and hyperalgetic extremity—may require a deviation from the widespread practice of advancing from conservative to invasive pain management (Prager).22 Notably, it is also important to remain vigilant over those patients lacking any significant maladaptive or pathological psychological conditions, as the future can be very unpredictable. Brief, but regular, post-implant office visits for the purpose of reinforcing and supporting positive changes may pay big dividends.

Panel Recommendations
The panel recommends a pretrial or preimplantation psychological consultation for patients with chronic noncancer pain being considered for IT for. The evaluation should highlight characteristics that may positively or negatively impact a trial or long-term therapy. The potential influence of identified psychological factors should be outlined to the patient and significant-other. In addition to identifying relevant psychological conditions and behavioral patterns, the consistency among the patient’s complaints, the psychological exam, and the clinical findings should be give careful consideration. Patients manifesting one or more of the characteristics listed in “Contraindications for Immediate Trial/Implant” of Table 1 should be considered with great caution. Individuals exhibiting attributes outlined in “Indications to Proceed with Trial/Implant” could be viewed as more appropriate candidates from a psychological perspective. The psychological evaluation should also assess the need for any pretrial, preimplantation, or postimplantation targeted psychological/behavioral interventions determined to be potentially beneficial in obtaining or sustaining a positive outcome. A multidisciplinary approach to patient selection should be undertaken wherever possible to account for the multifactorial nature of pain and to avoid isolation of the psychological
components. The psychological consultant should have some level of participation in the preimplant trial and/or follow-up to evaluate the utility of the assessment and help determine whether the therapeutic goals have been achieved.

Table 1. Psychological Factors Influencing Patient Selection* (Doleys 1997, Doleys 2003)

<table>
<thead>
<tr>
<th>Contraindications for Immediate Trial/Implant</th>
<th>Indications to Proceed with Trial/Implant</th>
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<tbody>
<tr>
<td>• Untreated significant addiction</td>
<td>• Generally stable psychologically</td>
</tr>
<tr>
<td>• Active psychosis with delusional/hallucinatory components</td>
<td>• Cautious</td>
</tr>
<tr>
<td>• Major uncontrolled depression/anxiety</td>
<td>• Effectively defensive</td>
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<tr>
<td>• Active suicidal or homicidal behavior</td>
<td>• Moderate levels of self-confidence and self-efficacy</td>
</tr>
<tr>
<td>• Serious cognitive deficits</td>
<td>• Realistic concern regarding “illness” and proposed therapy</td>
</tr>
<tr>
<td>• Severe sleep disturbances</td>
<td>• Mild depression appropriate to the situation</td>
</tr>
<tr>
<td></td>
<td>• Generally optimistic regarding outcome</td>
</tr>
<tr>
<td></td>
<td>• Ability to cope with flare-ups, complications, and side effects appropriately</td>
</tr>
<tr>
<td></td>
<td>• Appropriately educated regarding procedure and device</td>
</tr>
<tr>
<td></td>
<td>• Supportive and educated family/support person</td>
</tr>
<tr>
<td></td>
<td>• History of compliance and cooperativeness with previous treatment</td>
</tr>
<tr>
<td></td>
<td>• Behavioral/psychological evaluation consistent with patient’s complaints and reported psychosocial status</td>
</tr>
<tr>
<td></td>
<td>• Comprehends instruction(s) and other information</td>
</tr>
<tr>
<td></td>
<td>• Patient/significant other has appropriate expectation(s)</td>
</tr>
<tr>
<td></td>
<td>• Patient able/willing to “tolerate” medication adjustments with drug delivery system</td>
</tr>
</tbody>
</table>

*Based on experience and conjecture; not clinically or experimentally validated.

References.


Social Issues
Although none are likely to represent an absolute contraindication to intrathecal therapy, a number of social issues may be influential in the patient selection process. Patient demographics, activity level, insurance coverage, compliance issues, and the potential for opioid abuse are all likely to impact treatment outcomes.

Patient Demographics. Few data exist to suggest that patient demographics should play a meaningful role in patient selection for intrathecal therapy, either in support of or as a contraindication to treatment; however, there is some evidence regarding the effect of demographic factors on pain prevalence and response to opioids that may assist in identifying suitable candidates for therapy (Estes 2009, Green 2009). In particular, disparities in pain along racial and gender lines suggest some demographic variation among patients presenting with intractable chronic pain. Female gender and African American racial status, specifically, have been associated with greater pain severity and increased activity limitations due to chronic pain (Estes 2009, Green 2009). A secondary analysis of data from the Quality of Life, Health, and Valuation of Life by Elders research study found that African American participants reported greater pain and functional limitation than Caucasians (Estes 2009). Those with arthritis-related pain demonstrated that self-rated health, reported symptoms of depression, and the correlation between race and frequency of reported health conditions strongly predicted functional limitation; African American individuals were found to have an increased risk of impairment, based on the number of comorbidities present, as compared with Caucasian elders (Estes 2009). Similar to the apparent increased prevalence of chronic pain conditions among African American patients, a secondary data analysis of the National Comorbidities Study Replication found that women were more likely than men to experience frequent or chronic pain (64% vs 43%, respectively; \(P<.001\)) (Green 2009).

Like race and gender, age is not a selection criteria specified in the literature for intrathecal drug delivery. There are no age restrictions for intrathecal therapy, although empiric evidence suggests that age may influence a patient’s response to opioid administration. For instance, a retrospective chart review of 206 patients with severe chronic noncancer pain found that initial starting doses of long-acting opioids (eg, morphine, methadone, and oxycodone) were similar in patients 50 years of age or younger compared with those older than 50 years of age; however, the younger cohort eventually required doses that were more than double those of the their older counterparts to maintain effective analgesia (Buntin-Mushock 2005). Furthermore, only patients in the older cohort demonstrated a reduction in visual analog scale pain scores during the course of opioid therapy. These results suggest that older patients will require fewer dose escalations with intrathecal morphine, possibly because opioid tolerance develops more slowly in individuals older than 50 years of age (Buntin-Mushock 2005).

Activity Level and Lifestyle Considerations. Patients whose ability to work and lifestyle are significantly impaired by chronic pain are reasonable candidates for intrathecal therapy, as intractable pain often leads to unemployment or underemployment. An analysis of data from the National Outcomes Registry for Low Back Pain demonstrates the prevalence of disability among patients with chronic noncancer pain, reporting that only 3.7% of patients receiving an intrathecal drug delivery system were working full time prior to implantation, whereas 62% were not working at all or were working at a reduced capacity (Deer 2004). Additionally, the secondary data analysis using the National Comorbidities Study Replication found that people with frequent or chronic pain work fewer weeks (33.8 vs 40.6 weeks; \(P<.001\)) and had higher disability rates and more physical and mental health conditions than those without intractable pain (Green 2009).
Importantly, research indicates that intrathecal drug delivery systems can result in an improvement in activity levels. A study of 24 osteoporosis patients with chronic pain receiving intrathecal therapy reported substantial improvements in functional scores based on the Quality of Life Questionnaire of the European Foundation of Osteoporosis—a 30-question tool measuring functionality with regard to daily activities, domestic activities, ambulation, and self-perception of general health—from a mean 114.7 points prior to the initiation of therapy to 79.1 points at 1 year post-treatment follow up (Shaladi 2007). A retrospective study of 19 patients with chronic noncancer pain further demonstrates the potential improvement in functional status indicating that most participants reported good or fair improvements in activity following implantation of an intrathecal drug delivery system; of the 13 patients who were not retired prior to receiving an implantable device, 5 were able to return to employment (Njee 2004).

Healthcare Coverage and Patient Compliance Factors. The majority of commercial health insurers—as well as Medicare/Medicaid and workers’ compensation programs—provide coverage for the intrathecal modality when utilized for approved indications, as intraspinal analgesia is an FDA-approved, commercially available treatment for intractable chronic pain. Since prior authorization for treatment will likely be required, it is necessary to confirm that a patient’s coverage provides for both surgical implantation and on-going medication refills prior to initiating intrathecal therapy. A survey of 87 pain practitioners indicated that only one-quarter were satisfied with the reimbursement received from private insurance companies and approximately 35% were satisfied with reimbursement received from workers’ compensation plans; the vast majority (90.5%) believed that reimbursement for filling, refilling, and programming medication pumps was insufficient to cover practice costs (Deer 2009). Thus, the patient’s out-of-pocket expenses associated with treatment will vary by plan and may be significant. The patient’s willingness and ability to cover these expenses may influence which individuals are suitable candidates for treatment.

The patient’s capacity for complying with the medication refill schedule is also a crucial component of the intrathecal therapy selection process. Initially, pump refills and dose adjustments are required approximately every 8 weeks; however, over time patients who develop a tolerance to therapy may require refills more frequently, possibly as often as every 4 to 6 weeks (Deer 1999). Only patients who are willing and able to maintain their refill schedule—typically those who do not have cognitive, psychological, or socioeconomic barriers and who benefit from family support—should be selected for treatment (Krames 1997).

Recognition of Opioid Abuse. For the majority of patients, the risk of addiction to opioids is low (Sinatra 2006). A survey of more than 100 patients who were previously prescribed opioids for chronic noncancer pain (mean duration of 14 months) found the rate of addiction to be only 2.8% (Cowan 2003). Regardless, clinicians should assess every patient’s risk prior to administering treatment. To assist in this assessment, clinicians are advised to use validated screening methods, such as the 24-item Screener and Opioid Assessment for Patients with Pain (SOAPP), which is specifically intended for use with noncancer pain patients (Butler 2004). Also available is the self-administered Opioid Risk Tool (ORT) that measures a patient’s risk for addiction by considering factors commonly associated with the disease, including a personal or family history of substance abuse, age, history of preadolescent sexual abuse, and certain psychological conditions (Webster 2005). Particular consideration should be given to male patients and those younger than 55 years of age, as evidence has found these individuals to be...
more likely to abuse opioids (White 2005). An analysis using an administrative database of medical and pharmacy claims of 16 self-insured employer health plans found that 57% of opioid abusers were male and 52.6% of abusers were between 35 and 54 years of age (White 2005). Nearly half of all opioid abusers in this analysis also reported a chronic pain condition (White 2005).

Notably, more recent research suggests that intrathecal drug delivery systems may be beneficial in patients with opioid use disorders (Webster 2007; Shaladi 2007). Specifically, there is evidence that the incidence of morphine dependence and tolerance is lower via intrathecal delivery than with systemic administration (Shaladi 2007).

Panel Recommendation. Published research to date does not confirm a direct link between social factors and outcomes of intrathecal therapy, and therefore, consideration of these factors should not definitively support or contraindicate treatment. Nevertheless, certain considerations may provide insight into the potential effect and/or consequences of treatment; these associated social issues should be carefully weighed during the patient selection process.

References
Pharmacologic Issues

Why Use Compounded Intrathecal Drugs?

Having already failed to respond to conservative pain management techniques, patients requiring intrathecal therapy are in need of an individualized approach to treatment. To optimize therapy in these patients, management of pain and adverse effects often requires combinations of intrathecal drugs to achieve appropriate analgesia. In addition, patient-centered treatment regimens seek to reduce the number of pump refills, as this minimizes not only cost and inconvenience, but also risk of infection associated with the refill process. To limit refills, intrathecal drugs are frequently used at higher concentrations than are commercially available. As a result, clinicians tend to rely on compounding as a means of providing individualized intrathecal formulations.

Drug compounding is the mixture or modification of ingredients to prepare a specialized medication for clinical use. It includes dilution, reconstitution, admixture, repackaging, and many other manipulations of sterile products. Although compounding for many delivery routes may pose a minimal threat to patient safety, improperly prepared or contaminated drugs intended for direct administration into the central nervous system (CNS) could have catastrophic effects and are considered high risk. It is, therefore, essential that clinicians and pharmacists alike understand the drugs, preservatives, and other excipients used in formulating these preparations and that they observe proper compounding procedures at all times.

Safety Considerations

At present, preservative-free morphine sulfate (Infumorph®, Baxter; Astramorph®, AstraZeneca) and ziconotide (Prialt®, Elan) are the only drugs approved by the US Food and Drug Administration (FDA) for intrathecal therapy (Infumorph®, Astramorph®, and Prialt® product inserts).1-3 Intrathecal morphine is often prescribed in concentrations that exceed commercially available preparations (25 mg/mL) and thus requires modification prior to intrathecal use (Deer 2007).4 Morphine and ziconotide can also be used in combination with other drugs—such as clonidine, hydromorphone, bupivacaine, gabapentin, and fentanyl—when monotherapy is inadequate (Deer 2007).4 To ensure safety and efficacy, prescribing physicians and compounding pharmacists must consider a number of critical parameters, including compatibility, concentration and solubility, tonicity, stability, and sterility.

Compatibility. Many of the commercially available drugs that are FDA-approved for other injectable routes are not compatible for intrathecal use due to the presence of preservatives or other excipients that may be neurotoxic. Benzyl alcohol, phenol, formaldehyde, and methylparaben preservatives are all reported to be neurotoxic when used intrathecally (Baxter 1962; Hetherington 2000).5,6 Based on case reports, acetate buffers, ethanol concentrations of 10% or greater, pH levels below 4 or above 9, and certain drug products may also be unsuitable for intrathecal use (Medtronic Educational Brief).7 Neurologic complications have been identified following the use of intrathecal drugs containing trace contaminants (Jones 2002).8 To ensure that intrathecal therapies are free of potentially dangerous ingredients, both the prescribing physician and the compounding pharmacist should be aware of all components of a
formulation, particularly for admixtures, where the ingredients of each component drug must be taken into account.

*Concentration and Solubility.* As part of the FDA approval process, drugs are commonly tested at varying concentrations, and the safety of a drug must be demonstrated at concentrations that exceed the final approved strength. However, to maximize the interval between pump refills, drugs used for long-term intrathecal therapy may be compounded at concentrations exceeding the approved strength. One must carefully consider the safety of administering higher concentrations of drug to the intrathecal space, where the margin of neurotoxicity safety may be narrow (Ghafoor 2007).9

In addition to the issue of concentration-related toxicity, compounding drugs at higher concentrations may lead to precipitation. It is vital that known solubility limits be observed when high-concentration formulations are prepared. Because solubility is also affected by temperature, formulations must be prepared at temperatures that do not exceed body temperature to prevent precipitation of oversaturated solutions. Furthermore, solubility decreases when drugs are combined, and data regarding the solubility of drugs in admixtures are limited. Finally, drug efficacy and solubility are affected by pH (Yaksh 2004)10 and by the presence of ions such as chloride (Ghafoor 2007).9 both of which differ from drug to drug. Thus, careful attention must be paid to a number of factors that can affect drug concentration and solubility.

*Tonicity.* Ideally, intrathecal drug solutions should be isotonic to the cerebrospinal fluid (CSF) (approximately 300 mOsm/L) (Deer 2007, Hassenbusch 2004, Ghafoor 2007)4,9,11 in order to maintain isotonic equilibrium in the intrathecal space. The overall tonicity of a compounded drug depends on the sum of its components, and the ability of CSF movement to compensate for deviations in tonicity depends in part on the flow rate of the pump (Ghafoor 2007).9 To achieve satisfactory tonicity for high-concentration formulations and for drug admixtures, sterile preservative-free water may be more appropriate as a vehicle than sterile saline (Ghafoor 2007).9

*Stability.* The effort to minimize refills by increasing drug concentrations and increasing reservoir volumes raises the issue of drug stability. Drugs used for long-term therapy via an intrathecal pump must remain stable at body temperature for months; however, stability data are lacking for most intrathecal agents (with the exception of morphine), and the effects of drug admixtures on the stability of their individual components are poorly understood.

*Sterility.* The consequences of administering a nonsterile drug into the intrathecal space are obvious, and CNS infections following pump implantation have been linked to compound formulations (Ubogu 2003; Follett 2004).12,13 To ensure the quality and safety of intrathecal preparations, compounding should be performed in immaculately clean facilities that maintain high standards for air quality; it is also essential that compounding pharmacists have a thorough understanding of aseptic procedures.

**Regulatory Considerations, Standards, and Guidelines**

The practice of pharmacy is regulated at the state level, although certain aspects of compliance are overseen by the FDA (Breaux 1998; Crawford 2002; Thompson 2003).14-16 FDA regulation of compounding pharmacy is a controversial issue that revolves around the effort of physicians and pharmacists to ensure patient access to individualized therapies on the one hand, and the FDA’s view that all compounded drugs are new agents and thus unsafe without full testing on
the other. For reasons of time and expense, the use of individualized therapies often precludes complete safety trialing. Currently, compounding pharmacies are exempt from many FDA regulations that apply to drug manufacturing, but must remain state-compliant and are limited to compounding drugs pursuant to valid prescriptions for individual patient needs. They are not allowed to engage in large-scale “manufacturing” for future or unidentified patients. Several of the FDA’s concerns regarding drug compounding are particularly relevant for intrathecal therapy, specifically those pertaining to the use of higher-than-approved drug concentrations and the compatibility and stability of compounded drug admixtures.

Standards and guidelines for pharmaceutical compounding practices have been established by the United States Pharmacopoeia (USP [www.usp.org]) and the American Society of Health-System Pharmacists (ASHP [www.ashp.org]), both of which provide frequent revisions and updated bulletins online (ASHP 2003, Hung 2004, USP 2008). Many of the USP and ASHP guidelines pertain to the assurance of sterility. These agencies define 3 risk levels for compounded sterile products (CSPs) based on the probability of microbial or foreign material contamination. Current guidelines assign the highest risk level (Level 3) for all “CSPs that lack effective antimicrobial preservatives (ASHP 2003).” Since preservatives are contraindicated for intrathecal use, all intrathecal drugs are classified as high risk. The preparation of CSPs is covered in depth in USP General Chapter <797>, Pharmaceutical Compounding—Sterile Preparations (USP 2008).

In addition, Polyanalgesic Consensus Guidelines (Deer 2007, Hassenbusch 2004) have been established based on extensive literature reviews and expert panel discussions. These are invaluable resources to the practicing pain physician, as they address clinical and preclinical data for specific intrathecal drugs; provide rationale for drug selection, dosage, and concentration; and offer considerations for compounding above and beyond the USP and ASHP guidelines.

References
7. Medtronic Educational Brief October 2002/2.03a; MHRA Medical Device Alert 2003/007/023/121/003, issued October 2003.


IT Trialing
Implementation of an intrathecal (IT) therapy trial typically serves as a final step in the patient selection process due to current insurance requirements (eg, Medicare) and widespread physician practices. Traditionally, patient response to analgesic administration during a trial has been used to determine the potential pain relief from IT therapy and to gauge patient level of commitment to treatment. Despite immediate short-term benefits, the value of a trial as an accurate predictor of subsequent IT therapeutic success or failure is difficult to corroborate. Trialing as an extrapolative screening tool for IT therapy requires close examination of how effectively the process determines who should or should not receive IT therapy.

Trialing Methodologies. Although IT trialing is commonly utilized prior to device implantation, the methods and locations in which testing are performed vary greatly. Screening techniques are implemented via epidural or intrathecal delivery, with the selected treatment administered through single injection, multiple injections, or continuous infusion. A trialing method is selected largely based on the patient’s overall condition, the physician’s preference, availability of facilities, practice environment, and insurance/Medicare coverage provided (Prager 2001). An evaluation of the National Outcomes Registry for Low Back Pain found that most trials were performed at a hospital as an inpatient procedure (72%), as opposed to an outpatient procedure in a hospital or ambulatory surgery center (16% and 12%, respectively) (Deer 2004). More than half of the trials in this report utilized a continuous epidural infusion and the majority of patients received only morphine (Deer 2004). Results showed that the mean trial duration was 3.5±5.4 days (Deer 2004). Each trialing method has unique advantages and disadvantages, and the clinician must decide, which technique—if any—is best suited for the patient (Table).
Table. Screening Trial Methods: Advantages and Disadvantages

<table>
<thead>
<tr>
<th></th>
<th>Single Injection</th>
<th>Multiple Injections</th>
<th>Continuous Infusion</th>
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<tbody>
<tr>
<td></td>
<td>Epidural</td>
<td>Intrathecal</td>
<td>Epidural</td>
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<td>Advantages</td>
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<td>3. No PDPH</td>
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<td>Disadvantages</td>
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<tr>
<td>response</td>
<td>response</td>
<td>effect</td>
<td>drug effect</td>
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<tr>
<td>2. Systemic drug</td>
<td>2. PDPH may</td>
<td>2. Does not mimic</td>
<td>3. Labor intensive</td>
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<td>effect</td>
<td>interfere with</td>
<td>chronic drug</td>
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<td>PDPH = postdural</td>
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<td>puncture headache.</td>
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**Reassessing Trial Goals.** The goal of a trial is to assist clinicians in the identification of appropriate candidates for IT therapy. Positive quantitative or qualitative patient response to an IT opioid trial has routinely been thought to translate into successful long-term IT therapy. Trial success has traditionally been set at 50% or greater improvement in pain score, although standards for trial failure have been less concrete (Krames 1997). A trial measures pain relief using an accepted tool, such as the Visual Analog Scale, compared against baseline measurements to assess patterns of response and indications of adequate pain reduction—with minimal incidence of intolerable side effects—to help qualify the patient for pump implantation. The historical perspective on trial goals was originally shaped by a limited array of approved IT opioid agents (primarily morphine) and arbitrary end points related to their pharmacologic effects. However, advances in pain practice attributable to novel nonopioid IT agents have broadened treatment strategies and devalued the relationship between opioid trial response and long-term benefit. Furthermore, discrepancies among comparative pain relief data associated with opioid trial agents and other drug classes or combinations difficult to use in trial settings heighten the ambiguity of trial goals.
Trends in pre- and post-implantation response are frequently examined in the literature in an attempt to characterize the role of IT trials in the patient selection process. Limited data suggest that IT trials predict outcomes; the only data which suggest there is predictive value come from retrospective studies. For instance, in a retrospective study of 29 patients with noncancer pain, 86% of patients reported their pain relief to be better or excellent in comparison to their trial experience during a mean follow-up period of 31 months (Willis 1999). In another retrospective study of 86 patients with noncancer pain undergoing opioid trials, Domínguez et al identified possible patient trends in responsiveness during trials that are predictive of long-term IT requirements post-implantation (Domínguez 2002); however, lack of similar studies prevents this retrospective study from generalizing all trials as useful predictive steps. Furthermore, studies do not consistently demonstrate a positive relationship between a successful trial and subsequent therapeutic success. In a prospective study of 18 patients with noncancer pain, all subjects achieved a pain decrease of greater than 50% during trial with IT morphine or sufentanil; yet, following implantation, 39% of the same patients experienced no pain reduction during a mean follow-up time of 2.4 years (Hasenbusch 1995). Another study showed that patients attaining good pain relief through a single-dose trial may experience inadequate benefit from long-term IT infusion (Yoshida 1996). Additionally, in select patient populations, such as those with fibrosis, restrictions in the epidural space may distort trial results and misrepresent the level of response that could be obtained with a permanent pump (Krames 1997). Trial outcomes frequently lack consistency with actual therapeutic response, since good or inadequate pain relief demonstrated during an IT trial may not materialize once actual treatment commences.

**Limitations and Compounding Effects.** The inability of a trial setting to simulate conditions of the intended IT environment and anticipate effects of chronic treatment has impeded the solidification of best practices for trial protocols; common trialing methods incompetently approximate the planned mechanisms of treatment. Trial durations also have a considerable range, typically lasting several days, but spreading anywhere from a few hours to several weeks. The practice of tailoring trials around patient characteristics is a consequence of the lack of current evidence to stratify any particular method over another (Prager 2001). Despite the paucity of guidelines promulgated for IT trialing, published trial guides, expert consensus, and review articles have invariably called for an IT therapy trial to provide clinical rationale for permanent pump and IT catheter implantation (Medtronic 2004, Deer 2007; Knight 2007), yet fall short of adequately or accurately predicting long-term effectiveness. In one monograph detailing recommended trial protocols, a pump manufacturer acknowledges the limitations of a positive trial in its inability to “guarantee a positive longer-term outcome.” Although no current standards exist for IT trials and expectations vary immensely, the Polyanalgesic Consensus Conference 2007 panelists recommended the continuation of trialing using a strategy determined by the performing physician, until data deem the trials unnecessary (Deer 2007). In earlier statements, the Polyanalgesic Consensus Conference 2003 panelists addressed “the potential for varied effects from differences in dosage, infusion rate and concentration” and noted that “the time-consuming strategy of conducting trials systematically by varying only 1 parameter at a time might be best for judging drug effects, but is impractical in most clinical settings (Hasenbusch 2004).” In a retrospective chart review of 86 individuals treated with a rotation of long-acting opioids for noncancer pain, the first of 5 tried opioids was adequately effective in only 36% of patients (Quang-Cantagrel 2000). However, substitution of new opioids cumulatively increased the percentage of efficacy and tolerability, with the fifth
consecutive agent yielding response in 14% of patients (Quang-Cantagrel 2000). As demonstrated by the continued response in the remaining subsets of patients, efficacy rates associated with individual opioids did not provide predictive value for other opioids to safely improve analgesia (Quang-Cantagrel 2000). The same substitution process may offer similar advantages in the IT therapy setting to fully assess the potential benefit from IT opioids, increase patient likelihood of response, and maximize pain relief outcomes over time. The 2003 Polyanalgesic Consensus Conference panelists also conceded the difficulty of devising dosing guidelines that pertain to all patients given the currently available armamentarium for IT infusion (Hassenbusch 2004). The infinite potential combinations of drug admixtures and doses, occurring with increasing frequency, are impractical to assess during trials and could have effects which are additive, subtractive, or synergistic. Some newer IT agents, such as the calcium channel blocker ziconotide, cultivate new challenges in meeting trial criteria set by insurance companies. 

Unlike opioids, which produce their effect within hours of administration, ziconotide may require several days of administration to demonstrate effectiveness. Consequently, ziconotide trials may require more rapid titration than would otherwise be used for chronic administration and, unfortunately, rapid administration of IT ziconotide can produce therapy-limiting side effects (Caraway 2008). Thus, evolving pharmacologic options hamper the standardization of trial design.

Separation of the powerful placebo effects of therapy constitutes another trial limitation that compromises the assessment of efficacy and elimination of toxicity issues. The limited duration of most trials cannot rule out placebo effects, which may explain patient response to some trials of IT analgesics, but failure to sustain improvement upon initiation of therapy. Such instances further detract from the predictive value of trialing. Krames et al does not find placebo response sufficient to withhold actual treatment due to the lack of specificity of the response to an isolated trial with a selected agent (Krames 2001). The author recommends maximizing the duration of the trial to guard against a placebo response, while conceding that placebo effects can last up to a year (Krames 2001). Krames et al also acknowledge the impact of trial time on occurrence of complications, including the dressing and tubing changes which may exacerbate infection (Krames 2001). Several strategies have been offered to circumvent placebo-related effects during the trial period and obtain a more objective analysis of response. Levy et al proposed a 2-phase trial approach to quantitatively establish an optimal starting dose for pain relief, followed by a crossover double-blind placebo-controlled trial to eliminate potential physician or patient bias (Levy 1997). Good-to-excellent pain relief was reported by 73% of study participants post-implantation (Levy 1997). Although they present tactics to control for placebo response during the trial phase, studies that report positive response following initiation of pump therapy are limited by the absence of long-term data demonstrating continuous benefit after 1 year. In addition, subjects who do not exhibit a positive response during a given trial may respond to alternate drugs or combination therapies.

Trialing assessments are largely based on the assumption that patient response to opioids will be clearly defined. However, failure of pain relief to endure beyond the trial can also be accounted for by the development of tolerance and opioid-induced hyperalgesia, which cannot be evaluated during the brief trial period. Careful titration or rotation to other opioids or medication combinations are occasionally required to maximize analgesia and provide adequate pain relief, a strategy which is not usually a trial component and would require lengthy trial duration (Manfredi 1997). Trials are also restricted by their inability to eliminate risk for toxicity and adverse events associated with the invasive procedure, the opioid, or the modality. Perioperative
risks, including those conferred by the surgical procedure of implanting an infusion system, cannot be anticipated during a trial; these and other independent shortcomings associated with trialing warrant careful consideration before validating the role of an IT trial.

Panel Recommendations: Alternative Psychological-Based Strategies. Clinical studies have historically characterized IT therapy as well tolerated, providing analgesia that outweighs adverse events, which can typically be managed through careful patient selection and monitoring. For example, side effects of morphine can be managed by rotation to hydromorphone, addition of an agent such as bupivacaine, or reducing the morphine dose. In addition, one of the more significant risks of IT therapy is the development of a catheter-tip inflammatory mass that expands, leading to cord compression with signs of myelopathy (Hassenbusch 2002), which may be minimized by careful dose selection and positioning of the catheter. Thus, concentrating clinical management on tolerable post-implantation adverse effects by refining IT pump regimens would prevent unnecessary involvement of vulnerable patients in a trial period. To minimize the physical and psychological burden on the patient, better utilization of available IT safety and efficacy evidence—in combination with a strategic, multifaceted patient selection process—would serve as a practical alternative to trialing.

The panel recommends reconsideration of mandatory IT trials. The decision to conduct a trial should be left to the physician but there should not be a requirement for a trial. The recommendation is based on the fact that the predictive value of trials is unsubstantiated, the absence of long-term efficacy, the lack of demonstrated safety sufficient to outweigh trial risks, the inability of trial agents to simulate the infusion rate and volume of IT medications comparable to long-term administration, and the time limitations to sufficiently monitor patient response—including potential development of tolerance and opioid-induced hyperalgesia. Lack of compatibility with emerging agents and combinations for IT drug delivery and potential complications inherent to trials themselves (ie, the probability that an implantable pump may be associated with a smaller risk of infection than a temporary catheter) should also be considered in determining trial utility during the patient selection process. Alternatively, the panel recommends a heavier focus on psychiatric evaluation as outlined in the “Associated Psychological Considerations” section, than on IT trials to safely qualify patients for pump implantation. For patients with chronic nonmalignant pain, a psychiatric evaluation may be the most valuable screen before commencing treatment and, being less invasive, would carry less risk. The presence or absence of comorbid mental disease may be equally or more predictive of IT success than an IT trial.

References

**Economic Factors**

Pain affects a staggering number of individuals in the United States each year. An estimated 76 million adults 20 years of age or older report having experienced pain that lasted more than 24 hours, a number that exceeds the combined incidence of diabetes, coronary heart disease, stroke, and cancer (American Pain Foundation).\(^1\) Approximately 15% to 25% of adults report having chronic pain—commonly defined as pain that persists for 6 months or longer—at any given time; in patients older than 65 years of age, the prevalence escalates to 50% (Brennan 2007, Krames 1997).\(^2,3\) The economic consequences of chronic pain are also substantial, amounting to an estimated $100 billion annually in direct and indirect costs (American Pain Foundation).\(^1\) Although the clinical and economic effects of intractable pain undoubtedly warrant proper treatment, the most appropriate and cost-effective method of therapy is often less clear. Systemic opioid administration is preferred over more invasive intraspinal modalities (Deer 1999),\(^4\) since oral and intravenous opioid regimens are not associated with surgery-related adverse effects (eg, postoperative infection, wound infection, meningitis, and postdural puncture headache) and allow for a lower initial expenditure (Deer 1999).\(^4\) Yet, for patients who require a
more aggressive approach to therapy, implantable drug delivery systems may provide a cost savings when used to maintain long-term analgesia.

Economic factors greatly influence treatment choices and can potentially prevent the implementation of effective therapy. According to a 2009 survey of healthcare practitioners who actively utilize implantable drug devices, 40.5% of respondents identified the cost of pump implantation as the greatest economic barrier to providing intrathecal therapy (Deer 2009). Drug and refill fees were also an important deciding factor, considered to be the greatest deterrent to intrathecal delivery by 34.5% and 25% of respondents, respectively (Deer 2009). In fact, 87.2% of those surveyed believed the cost of intrathecal agents to be at least somewhat important during the patient selection process (Deer 2009). Other economic considerations may also interfere with patient access to therapy, including issues related to reimbursement and out-of-pocket expenses (Deer 2009).

Several analyses have been performed to determine the cost of treatment with an implantable device, as compared with more conservative therapeutic approaches; however, these studies date back 10 to 20 years and thus the data are not contemporary. Nonetheless, there is limited evidence suggesting that intrathecal therapy is a cost-effective option (Bedder 1991, de Lissovoy 1997, Kumar 2002). Using patient hospital financial service records and Homecare vendor quotations, an early analysis by Bedder et al of 20 chronic pain patients determined the total 6-month cost of utilizing an exteriorized system to be roughly $22,000 compared with an approximate total cost of $18,000 for drug delivery via an implantable device (Bedder 1991). Although cost of treatment at 3 months was similar for both systems, researchers reported that the cost benefits accrued to the implantable device during long-term therapy (up to 12 months) (Bedder 1991). A 1997 analysis by de Lissovoy et al of a large simulated cohort of patients with failed back surgery syndrome (N=1000) evaluated the cost effectiveness of intrathecal therapy compared with alternative medical management over the course of 36 to 60 months (de Lissovoy 1997). Factoring in expenses associated with managing adverse effects and the price of pump replacement due to battery depletion or mechanical failure, the cost of intrathecal therapy through a 60-month period was found to be lower than standard medical management ($82,893 vs $85,186, respectively) (de Lissovoy 1997). Researchers reported a similar cost savings in patients utilizing intrathecal therapy for up to 5 years (Kumar 2002).

In the absence of more recent cost analyses, the following example has been developed to provide a more current look at cost issues relating to intrathecal therapy. This model examines the cost of providing analgesia with high- or low-end intrathecal monotherapy—as compared with a brand name or generic oral regimen—assuming that all regimens provide equal efficacy. Based on the cost of monotherapy, Prialt® was selected as the high-end intrathecal treatment and morphine was chosen as the low-end intrathecal therapy. Clearly, patients often require combination therapy to achieve analgesia and many physicians now use intrathecal admixtures in clinical practice; in relation to this model, the cost of most combination therapies will fall between that of Prialt® monotherapy and morphine monotherapy. Table 1 outlines the average cost per month for therapy with intrathecal Prialt®, intrathecal morphine, an oral brand name drug regimen, and an oral generic drug regimen; Table 2 provides projected expenses for each regimen when utilized over 10 years.
Table 1. Cost Comparison of a High End and a Low End Intrathecal Medication Versus a Brand Name Oral Drug Regimen and Generic Drug Regimen (in months)

<table>
<thead>
<tr>
<th>Drug Regimen and Dose</th>
<th>Time (in months/30 days)</th>
<th>Average Cost ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intrathecal Prialt®</strong></td>
<td>0</td>
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<tr>
<td></td>
<td>1</td>
<td>$781.20</td>
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</tr>
<tr>
<td></td>
<td>12</td>
<td>$9,374.40</td>
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<tr>
<td><strong>Intrathecal Morphine</strong></td>
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</tr>
<tr>
<td></td>
<td>1</td>
<td>$50.94</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>$101.88</td>
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<td>$560.34</td>
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<td>$611.28</td>
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<tr>
<td><strong>Oral Brand Name Regimen</strong></td>
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<tr>
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<tr>
<td>Drug Regimen and Dose</td>
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<td>Average Cost ($)</td>
</tr>
<tr>
<td>-----------------------</td>
<td>--------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Oral Generic Regimen</td>
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<td></td>
</tr>
<tr>
<td>Methadone 10 mg QID</td>
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</tr>
<tr>
<td>Oxycodone 15 mg QID</td>
<td>2</td>
<td>$636.00</td>
</tr>
<tr>
<td>Gabapentin 400 mg QID</td>
<td>3</td>
<td>$954.00</td>
</tr>
<tr>
<td>Desipramine 10 mg TID</td>
<td>4</td>
<td>$1,272.00</td>
</tr>
<tr>
<td>Trazodone 50 mg QHS</td>
<td>5</td>
<td>$1,590.00</td>
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<td>6</td>
<td>$1,908.00</td>
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<td>12</td>
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<td>$34,272.00</td>
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Table 2. Cost Comparison of a High End and a Low End Intrathecal Medication Versus a Brand Name Oral Drug Regimen and Generic Drug Regimen (in years)\textsuperscript{9,12*}

<table>
<thead>
<tr>
<th>Drug Regimen and Dose</th>
<th>Time (in years)</th>
<th>Average Cost ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intrathecal Prialt®</strong></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Average dose 4 mcg/day in 20 mL Medtronics pump</td>
<td>1</td>
<td>$9,374.40</td>
</tr>
<tr>
<td>Medicare J2278 unit measure billing per 1 mcg</td>
<td>2</td>
<td>$18,748.80</td>
</tr>
<tr>
<td>ASP+6% = $6.51/mcg</td>
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<td>$28,123.20</td>
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<td></td>
<td>4</td>
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<td></td>
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<td></td>
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<td>$74,995.20</td>
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<td>$84,369.60</td>
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<td></td>
<td>10</td>
<td>$93,744</td>
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</table>

<table>
<thead>
<tr>
<th>Drug Regimen and Dose</th>
<th>Time (in years)</th>
<th>Average Cost ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intrathecal Morphine</strong></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Average dose 6 mg/day in Medtronics 20 mL pump</td>
<td>1</td>
<td>$611.28</td>
</tr>
<tr>
<td>Medicare J2275 unit measure billing per 10 mg</td>
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<td>$1,222.56</td>
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<td>ASP+6%= $2.8/10 mg</td>
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<td>$1,833.84</td>
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<td>$3,667.68</td>
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<td>$4,278.96</td>
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<tr>
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<td>$4,890.24</td>
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<td></td>
<td>9</td>
<td>$5,501.52</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>$6,112.80</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug Regimen and Dose</th>
<th>Time (in years)</th>
<th>Average Cost ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral Brand Name Regimen</strong></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Oxycontin 80 mg TID</td>
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<td>$34,272.00</td>
</tr>
<tr>
<td>Percocet 10/325 mg 8x day</td>
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<td>$68,544</td>
</tr>
<tr>
<td>Lyrica 150 mg BID</td>
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<td>$102,816</td>
</tr>
<tr>
<td>Cymbalta 60 mg QD</td>
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<td>$137,088</td>
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<tr>
<td>Klonopin 1 mg BID</td>
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<td>$171,360</td>
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<tr>
<td>Ambien CR 12.5 mg QHS</td>
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<td>$205,632</td>
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<tr>
<td></td>
<td>7</td>
<td>$239,904</td>
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<tr>
<td></td>
<td>8</td>
<td>$274,176</td>
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<td>$342,720</td>
</tr>
<tr>
<td>Drug Regimen and Dose</td>
<td>Time (in years)</td>
<td>Average Cost ($)</td>
</tr>
<tr>
<td>-----------------------</td>
<td>----------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Oral Generic Regimen</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

| Methadone 10 mg QID   | 1              | $3,816.00        |
| Oxycodone 15 mg QID   | 2              | $7,632           |
| Gabapentin 400 mg QID | 3              | $11,448          |
| Desipramine 10 mg TID | 4              | $15,264          |
| Trazodone 50 mg QHS   | 5              | $19,080          |
|                       | 6              | $22,896          |
|                       | 7              | $26,712          |
|                       | 8              | $30,528          |
|                       | 9              | $34,344          |
|                       | 10             | $38,160          |

As previous analyses have demonstrated, intrathecal therapy is associated with relatively high initial costs for device implantation, as well as monthly fees for pump refilling and/or reprogramming, regardless of which agent is administered (Tables 3-5) (Bedder 1991, Lissovoy 1997, Kumar 2002). Yet, even after factoring in these added expenses, intrathecal delivery of either Prialt® or morphine is less costly than a brand name oral regimen. As Figure 1 demonstrates, the cost of an oral brand name regimen exceeds that of intrathecal morphine after 7 months of treatment; after 10 months, intrathecal Prialt® is also found to be less expensive than brand name oral therapy. After 10 years of treatment, brand name oral therapy remains the most costly option (Figure 2). Generic oral therapy represents the least expensive treatment option when compared with a brand name oral regimen or intrathecal drug delivery regardless of the length of treatment; however, the use of only oral generics in clinical practice is rarely done. Instead, treatment with intrathecal morphine may provide a comparable alternative to the least costly generic oral therapy.

Notably, the data used in this example are based on intrathecal therapy with a programmable drug delivery system, as opposed to a constant flow device. At present, the US market largely utilizes programmable pumps because they provide a high level of patient satisfaction by allowing for dose adjustments that correspond with pain fluctuations. Medicare reimbursement varies for programmable and constant flow devices, thus costs may be different depending on the pump used.
### Table 3. Initial Pump Expense and Monthly Refill Costs

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Physician Reimbursement</th>
<th>Clinic Reimbursement</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening test</td>
<td>$89.00</td>
<td>$474.00</td>
<td>$563.00</td>
</tr>
<tr>
<td>Catheter insertion</td>
<td>$365.00</td>
<td>$2,777.00</td>
<td>$3,142.00</td>
</tr>
<tr>
<td>Pump placement</td>
<td>$384.00</td>
<td>$12,282.00</td>
<td>$12,666.00</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td></td>
<td><strong>$16,371.00</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Physician Reimbursement</th>
<th>Clinic Reimbursement</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refill</td>
<td>$87.00</td>
<td>$188.00</td>
<td>$275.00</td>
</tr>
<tr>
<td>Pump reprogramming</td>
<td>$51.00</td>
<td>$163.00</td>
<td>$214.00</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td></td>
<td><strong>$489.00</strong></td>
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</table>
Table 4. Monthly Costs, Including Initial Pump Cost and Refills*<sup>9-12</sup>

<table>
<thead>
<tr>
<th>Drug Regimen and Dose</th>
<th>Time (in months/30 days)</th>
<th>Average Cost ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intrathecal Prialt®</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average dose 4 mcg/day in 20 mL Medtronics pump</td>
<td>0</td>
<td>$16,371</td>
</tr>
<tr>
<td>Medicare J2278 unit measure billing per 1 mcg</td>
<td>1</td>
<td>$17,641.20</td>
</tr>
<tr>
<td>ASP+6% = $6.51/mcg</td>
<td>2</td>
<td>$18,911.40</td>
</tr>
<tr>
<td>Refills performed once a month</td>
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<td>$20,181.60</td>
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<td></td>
<td>4</td>
<td>$21,451.80</td>
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<td>$22,722</td>
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<td>6</td>
<td>$23,992.20</td>
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<td>$25,262.40</td>
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<td>$30,343.20</td>
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<tr>
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<td>12</td>
<td>$31,613.40</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug Regimen and Dose</th>
<th>Time (in months/30 days)</th>
<th>Average Cost ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intrathecal Morphine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average dose 6 mg/day in Medtronics 20 mL pump</td>
<td>0</td>
<td>$16,371</td>
</tr>
<tr>
<td>Medicare J2275 unit measure billing per 10 mg</td>
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<td>$16,910.94</td>
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<td>ASP+6% = $2.83/10 mg</td>
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<tr>
<td>Refills performed once a month</td>
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<td>$17,990.82</td>
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<tr>
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<td>4</td>
<td>$18,530.76</td>
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<td>$22,310.34</td>
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<tr>
<td></td>
<td>12</td>
<td>$22,850.28</td>
</tr>
</tbody>
</table>
Table 5. Yearly Costs, Including Initial Pump and Refills$^{9,12}$

<table>
<thead>
<tr>
<th>Drug Regimen and Dose</th>
<th>Time (in years)</th>
<th>Average Cost (in dollars)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrathecal Prialt®</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average dose 4 mcg/day in 20 mL</td>
<td>0</td>
<td>$0</td>
</tr>
<tr>
<td>Medtronics pump</td>
<td>1</td>
<td>$31,613.40</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>$46,855.80</td>
</tr>
<tr>
<td>Medicare J2278 unit measure billing per 1 mcg</td>
<td>3</td>
<td>$62,098.20</td>
</tr>
<tr>
<td>ASP+6% = $6.51/mcg</td>
<td>4</td>
<td>$77,340.60</td>
</tr>
<tr>
<td>Refills performed once a month</td>
<td>5</td>
<td>$92,583.00</td>
</tr>
<tr>
<td></td>
<td>6 (including a pump replacement $12,666)</td>
<td>$120,491.40</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>$135,733.80</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>$150,976.20</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>$166,218.60</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>$181,461.00</td>
</tr>
<tr>
<td>Intrathecal Morphine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average dose 6 mg/day in Medtronics 20 mL</td>
<td>0</td>
<td>$0</td>
</tr>
<tr>
<td>pump</td>
<td>1</td>
<td>$22,850.28</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>$29,329.56</td>
</tr>
<tr>
<td>Medicare J2275 unit measure billing per 10 mg</td>
<td>3</td>
<td>$35,808.84</td>
</tr>
<tr>
<td>ASP+6% = $2.83/10 mg</td>
<td>4</td>
<td>$42,288.12</td>
</tr>
<tr>
<td>Refills performed once a month</td>
<td>5</td>
<td>$48,767.40</td>
</tr>
<tr>
<td></td>
<td>6 (including a pump replacement $12,666)</td>
<td>$67,912.68</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>$74,391.36</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>$80,871.24</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>$87,350.52</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>$93,829.00</td>
</tr>
</tbody>
</table>
Figure 1. Cost Comparison of 2 Intrathecal Medications to an Oral Brand Name Medication Regimen and an Oral Generic Medication Regimen

*Hospital outpatient rates are based on the average standardized operating amount ($5128.41) plus the capital standard amount ($424.17), as published in the Federal Register, Volume 73, Number 193, October 3, 2008, CMS-1390-N. Physician payment is determined by multiplying the sum of the 3 component RVUs by the 2009 conversion factor ($36.0666), as published in the Federal Register, Volume 73, Number 224, November 19, 2008. Final reimbursement is adjusted by the Geographic Practice Cost Indices (Federal Register Number 193, Federal Register Number 224). \(^{13,14}\)

**Panel Recommendations.** Chronic pain management should always follow a step-wise approach—progressing to a more aggressive treatment as necessary—while considering associated financial cost. For those who meet all patient selection criteria for intrathecal therapy, an implantable drug delivery system may offer an alternative method to maintain pain relief without necessarily increasing the cost of care. However, even an appropriately selected patient will have poor outcomes if they are not properly managed, which will negate any potential cost benefit associated with intrathecal delivery.
References


REGIONAL TECHNIQUES FOR CANCER PAIN

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REGIONAL TECHNIQUES FOR CANCER PAIN
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INTRODUCTION

Pain is one of the most prevalent symptoms among patients with advanced cancer. It is the consequence they fear most and with good reason. Numerous studies have shown that 30-50% of all cancer patients undergoing chemotherapy or other antitumor treatments and 50-80% of those with advanced cancer suffer severe pain (von Gunten, 1999).

Exceeded only by heart disease, cancer is the second leading cause of death in the U.S. with 1 of every 4 deaths resulting from cancer. In 1999, the American Cancer Society estimated that 563,100 Americans would die of cancer - more than 1,500 people a day. Projections for the diagnosis of new cancer cases reached an all time high of 1,220,100. Therefore, even applying a conservative estimate of 50%, results in at least 610,050 new cancer cases that will require treatment for pain from cancer (American Cancer Society Website, 2000).

The consequences of cancer pain influence the functional capability and psychological well being of the cancer patient as the disease progresses (Bonica, 1990a; Jacox et al, 1994a &b). Providing relief is important not only as a humanitarian goal, but also to improve the patient’s prospects for survival. Unrelieved pain can significantly diminish the patient’s quality of life and, therefore, diminish the patient's willingness to continue treatment or even to continue living (Jacox et al, 1994a & b; Foley, 1996). Nearly 60% of Americans indicate they would favor physician-assisted death as a last resort to end suffering from uncontrolled pain associated with an illness (Blendon et al, 1992).

Drug therapy remains the foundation of cancer pain management. Numerous studies have demonstrated that the World Health Organization (WHO) three-step hierarchy for pain management is effective in controlling pain for 70-90% of patients with cancer (De Conno et al, 1993). However, for the 10% to 30% of cancer patients whose pain is not being controlled by the WHO three-step ladder or in patients that are experiencing severe side effects from the treatments, regional anesthetic techniques can be very valuable.

This chapter will discuss the role of regional anesthetic techniques for the treatment of cancer pain, the different pain syndromes that may affect the cancer patient and the regional anesthetic management of specific syndromes.

THE ROLE OF REGIONAL ANESTHETIC TECHNIQUES FOR THE TREATMENT OF CANCER PAIN

There is no clear consensus on when more invasive therapies should be used in cancer patients, but as a general rule of thumb, therapies should start with more conservative, low-risk procedures and progress to more invasive high risk procedures that are justified by the presence of severe refractory pain. The United States Agency for Health Care Policy and Research
(AHCPR) has published guidelines for the management of cancer pain (Jacox et al, 1994a &b). Although their report focuses more on the pharmacological management of cancer pain, they endorse the use of regional anesthetic techniques for the treatment of severe cancer pain. However, they are critical of the lack of well-controlled studies on the outcome of interventional techniques for cancer pain. In 1996, the American Society of Anesthesiologists published guidelines for the treatment of cancer pain that focused more on the regional anesthetic techniques (Ferrante et al, 1996). The take-home message from these published guidelines is “first do no harm”. If more conservative non-invasive measures have not been tried in the cancer pain patients, do not forge ahead to more invasive, high-risk procedures. As stated in the introduction, 70-90% of patients can be successfully treated with conservative measures outlined in the WHO three-step ladder. On the other hand, cancer patients who are suffering from severe unrelieved pain or are experiencing debilitating side effects from systemic therapy should not be denied the benefits of regional anesthetic techniques that can turn a major pain crisis into a manageable one (Lund, 1982). Table I summarizes the indications for regional anesthetic techniques in cancer pain.

**Local Anesthetic Neural Blockade**

Although temporary, local anesthetic neural blockade (LANB) is a valuable tool in the management of cancer pain (Abrams, 1989, Raj, 1993). Because the effects are temporary, the role of LANB must be clearly outlined to the patient, family and health care providers. It can be very distressing to the patient to have a significant pain relief with the LANB only to have the severe pain return after a few hours. Local anesthetic neural blockade (LANB) serves several purposes: 1) diagnosis, 2) prognosis, and 3) therapeutic.

**Diagnosis**

For diagnostic purposes, LANB can be very valuable in determining the pathway or mechanism of the pain. Table 2 gives examples of diagnostic blocks.

The anatomic source of the pain can be diagnosed with a variety of LANB. Joint pain resulting from cancer (i.e., osteonecrosis, sacroiliac joint metastasis) can be diagnosed with intra-articular injections. Muscle spasms as a result of tumor invasion of bony structures can be diagnosed with trigger point injections and peripheral nerve blocks can diagnose the peripheral neural pathway of the pain.

Although thoracoabdominal pain is often described as more localized and sharp as compared to thoracic and visceral pain, which is described as diffuse and dull, it can sometimes be difficult to differentiate visceral pain from thoracoabdominal wall pain, especially as the pain becomes more severe. For thoracic pain, intercostal blocks can differentiate between thoracic wall and visceral pain. With the exception of the cardiac structures, most of the sensory innervation of the thoracic viscera travels through the T1-T4 sympathetic ganglion. Therefore, cervicothoracic sympathetic blocks can be used to diagnose thoracic visceral pain. For abdominal pain, intercostal, celiac plexus and hypogastric plexus blocks can differentiate between abdominal wall and visceral pain.

Sympathetic blocks can be used to diagnose sympathetically mediated pain and guide treatment. Because somatic peripheral nerves contain both sympathetic and somatic fibers, it is necessary to block the sympathetic nervous system at locations that are free of somatic nerves.
This can be accomplished at the stellate ganglion for diagnosis of head, neck and upper extremity pain and at the lumbar ganglion for diagnosis of lower extremity pain.

The technique of differential blockade may be useful in cancer pain diagnosis. Since the description of this technique by Winnie and Collins, it has generated much controversy (Winnie and Collins, 1968). Both *in vitro* and *in vivo* studies have cast doubt on the existence of a differential effect of local anesthetics on varying sizes of nerve fibers. Although zones of differential sensory block after neuroaxial local anesthetics have been demonstrated in humans (Brull and Greene, 1989, 1991; Rocco et al, 1985; Greene, 1958), both *in vivo* and *in vitro* studies have produced conflicting results (Gasser and Erlanger, 1929; Gissen et al, 1980). Differential blockade can be achieved with different techniques: 1) spinal, 2) epidural, and 3) peripheral somatic blocks. All three techniques commonly use 2% lidocaine, which results in a motor, sensory and sympathetic block. The block is then evaluated as it regresses to determine if the pain correlates with the return of somatic sensory function or sympathetic function.

The use of placebo injections (i.e., saline) is controversial and should be used with caution in the cancer patient population. As many as one-third of the patients will respond to placebo and that does not necessarily mean that they do not have pain (Turner et al, 1994). In addition, saline injected into trigger points has been reported to be as effective as local anesthetic injections (Sola and Kuitert, 1955).

**Prognosis**

Prior to any permanent neurolytic procedure, it is recommended that a prognostic local anesthetic block of the nerve to be ablated be performed. An exception is for the terminally ill patient who incurs an extreme inconvenience during performance of the block. An example is a patient with terminal pancreatic cancer and severe pain who may experience severe discomfort from positioning during the block. Many practitioners would proceed with the neurolytic block in this setting. If numbness and motor blockade are unlikely to result from the block (i.e., celiac plexus block), it is more acceptable to proceed with the permanent neurolytic block without a diagnostic block.
The purpose of prognostic blocks is to allow the patient to experience not only the pain relief that may result from the block but also the numbness and motor blockade that may result. The numbness and motor blockade that results may be more distressing to the patient than the pain itself (Bonica, 1974).

Unfortunately, the prognostic value of long-term pain relief from a positive LANB is not guaranteed (Loeser, 1972). However, a negative LANB almost certainly will predict failure, thus supporting the use of the prognostic LANB prior to an ablative procedure (Raj, 1993).

Therapy

LANB is useful in the management of myofascial pain, sympathetically mediated pain, long-term treatments utilizing catheter techniques and continuous delivery, and in crisis management of severe pain.

Reflex muscle spasm caused by tumor invasion of deep tissues can be debilitating. Some patients will receive long-term benefit from trigger point injections of local anesthetics. If long-lasting benefit results, trigger point injections can be repeated at intervals of one to several weeks (Travell and Simons, 1983).

As tumors encroach on the nervous system, neural damage can result (Patchell, 1985). This neural damage can lead to complex regional pain syndromes that may be responsive to sympathetic blockade. It is known that the pain relief from such blockade can far outlast the duration of the local anesthetic (Bonica, 1979 and 1984). It is in these cases that the sympathetic blockade can be repeated at intervals of one to several weeks. Whereas the use of sympathetic blockade in chronic benign pain is focused more to improve function, the use of this technique in cancer pain is focused more on pain control.

Continuous LANB can be achieved by placement of catheters at peripheral nerve sites, epidurally, or intrathecally. The brachial and lumbar plexus are the most common sites for placement of peripheral nerve catheters. A case report on long-term continuous axillary plexus blockade demonstrated no adverse effects for up to 16 days (Sarma, 1990). Other sites that can be cannulated include the intercostal nerve, celiac plexus, hypogastric plexus, stellate ganglion and lumbar sympathetic ganglion (Ramamurthy and Winnie, 1985). The ease and low complication rate of epidural catheters favors this technique over peripheral nerve catheters for long-term pain management of localized pain (i.e., lower extremity, sacrum, upper extremity) (Du Pen et al, 1992). Even the chronic delivery of cervical epidural local anesthetics is safe and studies have shown that high concentrations of local anesthetic do not result in phrenic nerve block (Kasaba and Inoue, 1997). There are several studies on the use of intrathecal local anesthetics in combination with opioids for the treatment of cancer pain (Nitescu et al, 1990 and 1995; Sjoberg et al, 1991; Sjoberg et al, 1994; Van Dongen et al, 1993) with bupivacaine doses as high as 100 mg/day. It can be concluded from these studies that sensory-motor block does not occur at doses below 30-40mg/day. There is one case report on severe refractory cancer pain treated with daily intrathecal bupivacaine doses as high as 800mg/day (Berde et al, 1990).

Some cancer patients will develop severe pain that is refractory to opioid analgesics, even in high doses. These patients can benefit from continuous techniques to give them respite from the debilitating pain and allow a drug holiday from the opioids. This technique may also
provide pain control until palliative techniques such as chemotherapy, radiation therapy and radionucleotide therapy take effect.

**Steroid Injections**

Invasion or compression of nerves by growing tumors is a common source of pain. It is thought that inflammation plays a major role in the production of pain (Hanks et al, 1983; Elliot and Portenoy, 1998); however, other pain mechanisms responsive to the local application of steroids that have been postulated include a weak local anesthetic action (Seeman, 1966), a change in the activity in dorsal horn cells (Hall, 1982), and reduced ectopic discharge from neuromas (Devor, 1990; Johansson and Bennett, 1997). The local instillation of steroid in the compartment of the affected neural structure (i.e., brachial plexus, lumbar plexus, intercostal nerve) can result in significant and prolonged pain (Raj, 1993). If the tumor invades the vertebral column and compresses nerve roots, epidural steroid injections can be very helpful. A number of steroids may be used locally or epidurally which include methylprednisolone, triamcinolone, betamethasone, and dexamethasone (Benzon, 1992; Langmayr et al, 1995). Although not performed routinely, the intrathecal delivery of steroids has been used for lumbar radiculopathy. There is a concern of inducing arachnoiditis with this technique but many reports fail to show any serious adverse events (Langmayr et al, 1995; Feldman and Behar, 1961; Hartmann et al, 1974). A comprehensive review by Abrams and O’Connor concluded that most cases of arachnoiditis following subarachnoid steroid injections occur with multiple injections over a prolonged time period (Abrams and O’Connor, 1996).

**Neurolysis**

Neurolytic procedures are potentially very useful for patients with severe localized pain. Examples are gasserian ganglion block for facial pain, celiac plexus block for abdominal pain and intrathecal alcohol for dermatomal pain. The use of a single procedure for the treatment of pain has potential cost savings and is usually viewed favorably by the patients. However, there is no clear consensus on when to use neurolytic procedures for cancer pain management. Because of inherent risks associated with neurolysis, one must be reasonably certain that the outcome will be favorable.

The decision to perform neurolytic procedures for cancer pain control is based on 1) life expectancy, 2) pain description and location, and 3) pain mechanism (Patt, 1997). At best, the duration of pain relief from neurolytic procedures is on average 3 to 6 months. In addition, with long life expectancies, there is a risk of developing post-neurolysis neuropathic pain. Exceptions to post-neurolysis pain are 1) techniques that use more focused lesions (i.e.,, cryoanalgesia and radiofrequency thermal lesioning), 2) sympathectomy (i.e., celiac plexus, hypogastric plexus, stellate ganglion, lumbar sympathetic ganglion), and 3) intrathecal neurolysis. Therefore, the decision to use neurolysis in patients with a life expectancy of greater than 12 months should be made with caution. On the other hand, patients with imminent death who are experiencing severe pain may benefit from neurolytic procedures; however, some neurolytic procedures require special techniques (i.e., fluoroscopy) or unacceptable recovery periods that may cause an extreme inconvenience for the patient. Therefore, a careful discussion with the patient, family and health care team should ensue. If the neurolytic procedure can be done at the bedside, it is more favorable than requiring transport to another facility.
Patients who have a poor description of their pain or have diffuse pain are poor candidates for regional neurolysis. An exception is a patient who has multiple areas of pain but can clearly define a localized area of the dominant pain. However, these patients run the risk of then focusing on the lesser pain problem once the dominant pain is relieved.

Patients with nociceptive pain (i.e., bone pain, soft tissue pain, abdominal pain) usually respond to neurolytic procedures better than those with neuropathic pain (Brown, 1981). Because neuropathic pain often results in more central nervous system changes, neurolysis of peripheral nerves is often ineffective. Unequivocal positive results from a diagnostic block are important before proceeding with neurolysis in these cases.

For nerves that have a significant sensory motor function (i.e., cervical and lumbar nerve roots), aggressive neurolysis may result in debilitating motor dysfunction. Pulsed radiofrequency (RF) lesioning is a recently described technique that delivers an electromagnetic field without producing neurodestructive heat (Sluijter et al, 1998), therefore, leaving sensory motor function intact. The pulsed fashion results in a silent period, which eliminates the heat that has been produced during the active cycle. This technique permits the delivery of a higher generator output without raising the tip temperature above 42 °C. This technique can be applied to a variety of peripheral nerves without the risk of motor dysfunction. After nerve injury, persistent small afferent fiber activity originates from the dorsal root ganglion after an interval of days to weeks; therefore, it is a reasonable approach to use this technique directed at the dorsal root ganglion (Wall and Devor, 1983). Pulsed RF lesioning has been reported to provide long-term pain relief in both lumbar and thoracic radicular pain (Munglani, 1999). The advantage of this technique is the minimal tissue destruction, which has a lower chance of deafferentation pain. The exact mechanism of pulsed RF lesioning is unknown.

The technique of pulsed RF lesioning for the treatment of postmastectomy pain is as follows. The uninsulated portion of the insulated RF needle should be bent approximately 45°. Manufactured pre-bent needles are recommended, as there is less of a chance of damaging the electrode tip. The tip of the needle is advanced into the neural foramen using the curvature of the tip to guide the needle into place. On lateral view, the tip should be located in the superior and posterior portion of the neural foramen, which is the location of the dorsal root ganglion (Figure 1). The lesion is created using a pulsed RF (300 kHz) for 30 milliseconds out of a 1 second cycle. The tip temperature should not exceed 42 °C and the duration is 120 seconds. A percutaneous sterotactic laminar osteotomy has been described and may be required to reach to the thoracic dorsal root ganglion.
Intraspinal Drug Therapy

Determining the efficacy of intraspinal drug therapy for cancer pain remains one of the greatest challenges in pain management. To date, there are no prospective randomized studies evaluating the efficacy of drug therapy for cancer pain. All studies rely on retrospective reviews of large numbers of patients with a limited duration of follow-up.

One of the reasons for the lack of controlled trials is that the high cost and invasiveness of such treatment ethically precludes a double blind, placebo controlled study design. Therefore, we can only rely on the retrospective reviews of patients receiving this therapy and attempt to make conclusions on the efficacy of this treatment. There is currently a randomized controlled trial comparing intrathecal drug therapy with conventional medical management for cancer pain. This may allow for better conclusions on the true efficacy of this important therapy.

Barriers to intraspinal drug therapy include: 1) requirement of specialized care (i.e., neurosurgeon or anesthesiologist) for placement and management; 2) high-cost of the implanted device; and 3) limited day to day flexibility of this technique. Therefore, a single pain relieving procedure, such as neurolysis, will likely be viewed more favorably. However, as discussed above, neurolysis has limitations that may result in intraspinal drug therapy being the treatment of choice.

The decision to start intraspinal drug therapy is based on: 1) pain location, 2) pain mechanism, and 3) life expectancy. In contrast to neurolysis, intraspinal drug therapy may be effective in more generalized pain. This is because the drug will diffuse throughout the intrathecal space to reach receptors located at multiple levels of the spinal cord. As discussed above, neurolysis is less effective for neuropathic pain. Therefore, intraspinal drug therapy may be more effective in these cases. The location of the pain will influence the technique of delivery. Pain that is localized and unilateral is often better managed with the epidural delivery of opioid/local anesthetic combinations. However, if the life expectancy is greater than 3 months, epidural delivery may be more costly and less effective over time because of epidural fibrosis (Arner et al, 1988). Pain that is more diffuse is better managed with intrathecal drug delivery. Since neuropathic pain is often less responsive to the opioids (Arner and Meyerson, 1988; Samuelson et al, 1995), other drugs such as clonidine (Eisenach et al, 1995), or
bupivacaine (Nitescu et al, 1990 and 1995; Sjoberg et al, 1991; Sjoberg et al, 1994; Van Dongen et al, 1993) may be more effective.

There is no lower or upper life expectancy limits for intraspinal drug therapy. However, life expectancy will influence the technique used to deliver the intraspinal drug based largely on costs of therapy. There are basically three types of intraspinal delivery techniques: 1) an externalized system; 2) a partially externalized system; and 3) a totally implanted system (Wallace and Yaksh, 2000). Each technique has different risks and costs that are taken into account when deciding which approach to use. Bedder et al compared the cost of the epidural morphine delivered via an external pump to intrathecal delivery. They concluded that although the initial costs for an intrathecal pump implant are higher (1.67 times higher), the break-even point appeared at 3 months and at 1 year the total charges for the epidural group were approximately twice as high as the intrathecal group (Bedder et al, 1991). Therefore, the following general rule can be applied: 1) life expectancy of less than 1 month - percutaneous catheter and external pump; 2) life expectancy of 1 to 6 months - implanted port and external pump, and 3) life expectancy of greater than 6 months – totally implanted system.

**CANCER PAIN SYNDROMES**

**Bone metastasis**

Bone metastasis is the most common cause of cancer related pain (Patt, 1993a). Many common malignancies, such as breast, prostate, lung, kidney, and thyroid, have a propensity to metastasize to the bone. Although the overall incidence of bone metastasis is about 66% (Patt, 1993a), the incidence of bony metastasis of breast and prostate cancer may be as high as 90% (Rosier et al, 1997). Although there is a high incidence of bone metastasis, the majority are nonpainful (Pollen and Schmidt, 1979). Bone pain may also result from cancer treatment such as osteonecrosis secondary to corticosteroid therapy and radiation therapy (Engel et al, 1981; Elliot and Portenoy, 1998).

Bone pain is often described as constant and exacerbated with movement. Because the bone is a deep structure, it is often described as a dull, deep ache with referred pain to other areas of the body. There may be spasms of the muscle that support the affected bone.

A bone scan is more sensitive than plain roentgenograms since up to 50% bone decalcification must be present for plain films to detect a lesion. It has been estimated that up to 50% of bone metastases detected by bone scan are not detected by plain roentgenograms (Harrington, 1988). However, in certain malignancies such as bone cancers, multiple myeloma and thyroid cancers, plain roentgenograms may be more sensitive (Edeiken and Karasick, 1987). In addition, bone scans may be falsely negative in the following: 1) areas of previously irradiated bone metastasis as the lesion becomes “burned out”, 2) lesions that are predominately osteoclastic, 3) in breast, lung, and prostate cancers, and 4) at certain hidden sites such as the T1 vertebral body, base of the skull, and sacrum (Thrupkaew et al, 1974; Patt, 1993). When evaluating bone scans, other causes must be ruled out such as infection, trauma and degenerative changes.

The causes of bone pain are unclear; however, it is known that bone structures are highly innervated, especially the periosteum (Hill and Elde, 1991; Hukkanen et al, 1992). It is likely that the mechanism of bone pain is both mechanical and chemical. Mechanisms of the pain from
bone metastasis include: 1) release of algogenic substances (prostaglandins, bradykinin, substance P, histamine) from the damaged bone tissue that stimulates free nerve endings; 2) stretching of the periosteum and fascia by increasing tumor size; and 3) pathologic fracture (Nielsen et al, 1991; Scher and Yagoda, 1987).

**Vertebral Metastasis**

The bony spine is the most common site of bone metastasis, especially breast, lung, prostate and kidney tumors (Harrington, 1988). Vertebral metastases deserve special attention because of the proximity to major neural structures (i.e., nerve root, spinal cord). Because of this proximity, vertebral metastasis can lead to serious spinal neuropathic syndromes.

Focal back pain is the earliest sign of vertebral metastasis (Rao et al, 1992). At this stage, local palpation of the vertebrae increases the pain. As the tumor grows, pain can be referred to other areas such as the sacroiliac joints, iliac crest, abdomen or pelvis (Stubgen, 1996). If epidural extension occurs, nerve root compression may result in radicular pain in the affected dermatome. Radicular pain is often unilateral in lumbar and cervical metastases and bilateral in thoracic metastases (Ruff and Lanska, 1989). As the tumor continues to grow, spinal cord compression can result in sensory-motor changes, autonomic dysfunction and severe pain. The pain of spinal cord compression is often described as burning and dysesthetic below the level of the compression (Elliott and Portenoy, 1998). Intramedullary cord metastasis usually results in a rapid progression of neurological deficit in a matter of days to weeks (Grem et al, 1985).

**Neural Compression/Invasion**

The cervical, brachial and lumbar plexus are vulnerable to compression from metastatic tumors. The brachial plexus is quite vulnerable to metastatic breast cancer, metastatic melanoma and superior sulcus lung tumors (Elliot and Portenoy, 1998). Lumbar plexus compression can result from cervical, rectal or metastatic cancer.

Pain is often an early sign of plexus compression and often precedes any neurological deficits. The pain is characterized as a diffuse ache in the distribution of the plexus innervation and progresses to dyesthesia, allodynia, muscle weakness, and sensory loss as the tumor infiltrates the neural structures (Foley, 1985).

Plexopathies must be differentiated from spinal metastasis and compression. Radiological investigations of the spine and pelvis are the gold standard in differentiating the two.

**Visceral Pain**

The abdominal viscera are innervated structures that can lead to pain when diseased. The most common causes of visceral pain include liver cancer, metastasis to the liver, and pancreatic cancer. Pain is present in approximately 80% of pancreatic patients prior to death (Horton, 1989). Visceral pain is often described as dull, diffuse and poorly localized. There is often
reflex muscle spasm in the paraspinal muscles or the abdominal wall as well as cutaneous hyperalgesia in the dermatomes that converge centrally with the innervation of the diseased organ. Liver pain is often referred to the epigastrum, and if diaphragmatic irritation occurs, the pain is often referred to the shoulder. Pancreatic pain is often referred to the epigastrum and back.

**Cancer Treatment Related Pain**

**Postmastectomy Pain** – Up to a third of women develop pain as the result of treatment of their breast cancer (Wallace et al, 1996). The pain is often described as a general burning and aching sensation referred to the axilla, medial upper arm, and/or chest. There may be paroxysmal episodes of shooting and lancinating pain. In addition, some women may report phantom breast pain, mainly in the nipple. The pain may be exacerbated with arm movement leading to a frozen shoulder as the patient attempts to keep the arm in a flexed position close to the chest wall. The intercostobrachial nerve has been reportedly injured in 80-100% of mastectomy patients undergoing axillary dissection and has been described as the cause of the axillary and upper arm pain (Wallace et al, 1997). Phantom breast pain occurs in 10-64% of women with most of the phantom pain and sensations reported in the nipple. This is because the nipple is the most highly innervated breast tissue. It is supplied by the fourth intercostal nerve (Kroner et al, 1992). Other causes of postmastectomy pain include the following: 1) damage to the long thoracic nerve leading to denervation of the serratus anterior muscle, winged scapula and musculoskeletal pain in the shoulder girdle; 2) damage to the thoracodorsal nerve leading to denervation of the latissmus dorsi and musculoskeletal pain; and 3) mastectomy scar pain, which is described as painful and dysesthetic (Wallace et al, 1997; Scov et al, 1990). Table 3 summarizes the causes of postmastectomy pain.

**Postthoracotomy Pain** – The incidence of chronic postthoracotomy pain ranges from 26-67%. The pain is often described as a general burning and aching along the chest wall surrounding the surgical scar. There may be associated scar pain and myofascial pain involving the chest wall. The etiology of postthoracotomy pain is thought to be secondary to surgical trauma to the intercostal nerve (Wallace, 1997).

**Post Radical Neck Dissection Pain** – Many patients will develop pain after radical neck dissection. The pain is described as a sensation of tightness, burning and dyesthesis in the shoulder, neck and jaw. Lancinating type pains are occasionally reported (Sist et al, 1999). The etiology of the pain is likely secondary to damage to the cervical nerves and cervical plexus during surgery. Shoulder pain can result from loss of normal support to the shoulder secondary to loss of the neck musculature leading to musculoskeletal pain (Swift, 1984). It has been suggested that the cervical plexus provides some innervation to the trapezius and if damaged can lead to chronic shoulder and arm pain (Krause, 1992). In addition, damage to the spinal accessory nerve has been shown to increase the risk of chronic shoulder pain. This can result in loss of innervation to the trapezius muscle and musculoskeletal pain in the shoulder girdle (Terrell et al, 2000). Damage to the auriculotemporal nerve after cancer surgery has been reported to lead to gustatory sweating, hyperemia and pain (Hanowell et al, 1979).

**Phantom Limb and Stump Pain** – Phantom limb pain is a well-described pain syndrome with an incidence as high as 85% in the first 12 months after surgery. Sixty percent of patients continue to have pain one year after surgery. The incidence increases with more proximal amputations. It
occurs most often in the amputated extremities; however, phantom pain may occur in any appendage (i.e., tongue, penis, breast, nose). It is more common in patients that have preamputation pain. Phantoms often assume painful postures that eventually telescope into the stump. Phantom and stump pain is often described as burning and dysesthetic with intermittent lancinating pains. Stump pain is differentiated from phantom pain in that the etiology is often due to abnormalities at the stump site such as bone spurs, osteomyelities, myofascial trigger points or neuromas (Foley, 1987). Traumatic neuromas account for approximately 20% of stump pains.

Post-Radiation Pain Syndromes – Radiation therapy for the treatment of cancer can result in debilitating pain. Severity and time of onset is proportional to the total dose (Johnstone et al, 1995; Parsons et al, 1994; Vujaskovic et al, 1995). Major plexi are exceptionally susceptible to radiation neuritis. For example, radiation to the axilla essentially encompasses not only the local innervation but the cords of the brachial plexus. The mechanism of pain is thought to be secondary to damage to the microvasculature of the nervous system resulting in ischemia. Electron microscopy of the sciatic nerve 12 months after radiation showed a significant decrease in nerve fiber density, primarily the large fiber population. In addition, an increase in microtubule and neurofilament density was observed. Other mechanisms include fibrosis of the connective tissue leading to nerve compression, demyelination, and chronic inflammation of the connective tissue (Wallace et al, 1997). The pain is often described as burning and dysesthetic. Radiation-induced pain can be delayed for years after treatment (Gillette et al, 1995).

Post-Chemotherapy Pain Syndromes – Peripheral neuropathy is the most common pain syndrome secondary to chemotherapy. The agents most commonly causing peripheral neuropathy include the vinca alkaloids, cisplatinum, procarbazine, misoniadazole and hexamethylmelamine (Mollman, 1988). The pain is usually described as burning, dysesthetic and localized to the hands and feet. Occasionally, it may progress to a sensory and motor neuropathy.

HEAD AND NECK

Overview

Pain related to a malignant neoplasm of the head and neck poses one of the most challenging pain management problems due to the overlapping sensory innervating of the area. Most of the pain can be managed with medical regimens; however, neural blockade can be a very effective addition (Carron, 1981; Shapshay et al, 1980; Rizzi, 1975; Bonica and Madrid, 1979). Sensory innervation of the head and neck arises from the cranial nerves V, VII, IX and X, and dorsal roots of the second, third and fourth cervical nerves. Sympathetic innervation derives from the T1 and T2 spinal cord segments. Preganglionic sympathetic axons exit the ventral roots of T1 and T2 and then travel as white communicating rami before joining the sympathetic chain and to synapse at the inferior (stellate), middle, or superior cervical ganglion. Postganglionic nerves either follow the carotid arteries to the head or integrate as the gray communicating rami before joining the cervical plexus or upper cervical nerves to innervate structure of the neck. Use of local anesthetic blocks help to localize the relative contribution of individual nerves to the painful area and subsequent neurolytic blockade can be considered to prolong pain relief.
Deep and Superficial Cervical Plexus Blockade

The dorsal roots of the second, third, and fourth cervical nerves pass posteriorly to the vertebral artery as they exit the intervertebral foramen. The anterior branches of the cervical nerves join to form the cervical plexus. The superficial branches including the lesser occipital, the greater auricular, the transverse cervical and supraclavicular nerves travel posteriorly to the sternocleidomastoid (SCM) muscle through the cervical fascia to provide cutaneous sensory innervation. The lesser occipital nerve (C2, C3) passes superiorly from the posterior border of the SCM muscle to innervate the supralateral aspect of the neck, the upper pole of the ear, and the occipital region of the scalp. The greater auricular nerve (C2, C3) travels anterosuperiorly from the posterior border of the SCM muscle before dividing into anterior and posterior branches. The anterior branch supplies cutaneous innervation to the posterosuperior face, whereas the posterior branches innervate the mastoid process and lower pole of the ear. The transverse cervical nerve (C2, C3) passes anteriorly from beneath the external jugular vein and supplies cutaneous innervation over the anterolateral aspect of the neck from the mandible to the sternum. The supraclavicular nerve (C3, C4) also exits posteriorly to the SCM to innervate the lower neck to the acromioclavicular junction, as well as to the anterior chest to the level of the second rib. (Waldman & Winnie et al, 1996; Brown DL, 1992). The greater occipital nerve is the dorsal branch of the second cervical nerve and is not a part of the cervical plexus.

The deep branches of the cervical plexus supply sensory innervation to musculature, bony and articular structures of the neck. (Carron H et al, 1984)

Superficial Cervical Blockade

For occipital and posterior auricular neuralgia due to acute inflammation or tumor compression, a superficial plexus block and/or a greater occipital nerve block is indicated. The patient is placed in supine position, and the neck is flexed and rotated to the contralateral side of the blockade. The posterior borders of the SCM muscle and external jugular vein are identified. At the location where the external jugular vein passes the posterior border of the neck, a 25-gauge, 4-cm needle is inserted subcutaneously immediately posterior and deep to the SCM. Along the posterior border of the SCM, 10 to 20 ml of local anesthetic is injected. (Masters, RD, et al, 1995; Cousin MJ et al, 1998)

Deep Cervical Plexus Blockade

A deep cervical plexus block is indicated for pain in the neck and occiput due to compression of the cervical plexus by tumors or metastatic lesions to the deep structures of the neck. With the patient in the supine position and the head turned to the contralateral side of the block, a line is drawn from the mastoid process to the anterior tubercle of the C6 transverse process at the level of the cricoid cartilage. Points marked 1.5, 3 and 4.5 cm inferior to the mastoid process along the line will correspond to the location of C2, C3 and C4, respectively. A 25-gauge, 8 to 9 cm needle is inserted until either the transverse process is contacted or paresthesia is encountered. Following negative aspiration, 2 to 4 ml of local anesthetic is injected at each of the three locations (Brown, 1992). An alternative approach of the cervical plexus block can be performed with a single injection after localization of the cervical plexus with a nerve stimulator.

The most common complication of the cervical plexus block includes the blockade of the phrenic nerve, which may lead to respiratory distress due to paralysis of the hemidiaphragm. Therefore, bilateral deep cervical plexus blockade is not recommended. Intravascular injection and subsequent signs of local toxicity may develop, if careful needle placement and aspiration...
are not carried out prior to the injection. Puncture of the dural sleeve and subsequent subarachnoid injection may occur and lead to total spinal blockade (Cousin et al 1998; Moore, 1967, Waldman, 1996; Bonica JJ, 1990b).

**Continuous cervical plexus block**

A continuous cervical plexus block can be readily achieved with the placement of a catheter in the superior portion of the interscalene groove. A local anesthetic will track superiorly to reach the nerve roots that supply the cervical plexus (Winnie, 1975). However, a local anesthetic will also reach the brachial plexus, which may result in upper extremity weakness. The negative effects of this weakness will need to be balanced with the positive effects of analgesia to determine efficacy. In addition, the phrenic nerve is frequently blocked with this technique but is seldom of significance with unilateral blocks. However, prolonged blocks may result in poor ventilation of the ipsilateral lung, leading to atelectasis. Therefore, it is recommended that intermittent injections rather than continuous infusions be used.

**Neurolysis of the Cervical Plexus**

Although neurolysis of the cervical plexus has not been described, intermittent interscalene neurolysis has been performed for tumors of the upper extremity via the interscalene approach. Case reports by Mullin and Neill discussed using 3% phenol and 50% alcohol, respectively, with minimal neurological sequelae (Mullin, 1980; Neill, 1979). Therefore, theoretically, cervical plexus neurolysis is possible with placement of the agent in the upper interscalene groove.

**Cervical Epidural Infusions**

For neck pain that does not respond to intermittent regional anesthetic techniques, a continuous cervical epidural should be considered. A cervical epidural infusion can be accomplished with a percutaneous temporary catheter with the infusion of low concentrations of bupivacaine (1/32% - 1/10%). The tip of the catheter should be placed as close as possible to the dermatomes supplying the cervical plexus (C2-4). Cervical epidural anesthesia (CEA) for head and neck pain has been reported to be an adequate and safe technique (Catchlove and Braha, 1984). Many avoid this technique because of fear of inducing a bilateral phrenic nerve block and respiratory distress. Although this is a theoretical consideration, studies have shown that a clinically significant phrenic nerve block does not occur even with high concentrations of local anesthetic. However, actual phrenic nerve activities show a suppression of 72% and 57% of control value with 1% and 2% lidocaine, respectively (Kasaba and Inoue, 1997). Studies on the effect of CEA on respiratory function have failed to show a significant effect on pO2, although most studies show a significant increase in pCO2 (Huang et al, 1990; Santanche and Goedecke, 1989). The most common effect of CEA is a decrease in heart rate and blood pressure. There is also a blunted response to atropine and atropine-like drugs (Biboulet et al, 1995; Arakawa et al, 1993). Therefore, close hemodynamic monitoring should be done in the first 24-48 hours.

**Stellate Ganglion Block**

The stellate ganglion, which consists of the inferior cervical and first thoracic ganglion, lies just anterior to the transverse process of the seventh cervical vertebra and lateral to the trachea. A blockade of the stellate ganglion will produce an ipsilateral sympathetic blockade of the head, neck, upper extremity and chest as well as sensory block of the anterolateral cervical
vertebrae. The development of Horner’s syndrome, which consists of miosis, ptosis and enophthalmos, ipsilateral facial anhidrosis and conjunctival injection, may confirm a sympathetic block of the head and neck, but not necessarily the upper extremity because some thoracic sympathetic preganglionic fiber which also innervates the upper extremities, lies in the higher thoracic ganglion at the T1 and T2 levels and bypasses the stellate ganglion (Cousin et al, 1998; Raj et al, 1996).

There are many indications for the use of a stellate ganglion block for the treatment of head and neck cancer pain. These include pain resulting from herpes zoster, postherpetic neuralgia (Currey and Dalsania, 1991), cervical vertebral metastasis, neuropathic pain secondary to chemotherapy or radiation therapy, pain from central nervous system lesions, and complex regional pain syndrome type I and type II (Arden et al, 1998). Response to stellate blockade with local anesthetic can serve as a diagnostic indication that pain transmission can be due to autonomic contribution. In addition, the initial response to the block will also serve as a prognostic indicator for possible repeated local anesthetic blocks, neurolytic block, or surgical intervention.

Anterior Approach at the sixth cervical vertebrae (C6)

At the beginning of the procedure, the patient is asked to lie supine with the placement of a thin shoulder roll so that the patient’s neck is extended to facilitate finding the appropriate anatomical landmark for performing the injection. First, the cricoid cartilage, which is at the C6 level is located just 1 to 1.5 cm lateral the cricoid cartilage and medial to the carotid pulse. The C6 transverse process, which is known as Chaussignac’s tubercle, can be palpated by applying firm pressure with the index and middle fingers of the nondominant hand of the operator. The skin is prepared antiseptically. With the index and middle fingers of the nondominant hand, the common carotid artery is gently retracted laterally. A skin wheal is made with injection of 1 % lidocaine with a 25-gauge 1- to 2-cm needle. Followed by that, a 25-gauge 4- to 5-cm needle is advanced perpendicular to the coronal cervical plane into contact with bone. The needle is then fixed in position with the index and middle fingers of the nondominant hand. The depth of the needle rarely exceeds 2.0 to 2.5 cm. Prior to the injection, the needle is withdrawn 2 to 5 mm and aspirated to assure no CSF or blood return, and thus minimizing the risk of intravascular or intrathecal injection. If the aspiration is negative, 0.5 to 1.0 ml of solution is administered to assess the absence of adverse events. Since talking may cause needle dislodgment and patient discomfort, instructing the patient to point his or her index or thumb upward may be a safer and alternative way to communicate with the patient during the procedure. After the initial test dose, a total of 8 to 10 ml solution can be injected in 2 to 3 ml increments with frequent aspiration. (Waldman et al,1996, Hahn et al, 1996)
Anterior approach at the seventh cervical vertebrae (C7)

Similar approach can be used at the C7. Since C7 turbecle is difficult to palpate, one must find the Chaussignac's turbecle first, then move caudally one fingerbreadth to locate the C7 turbecle. A pillow can be placed under the shoulders to extend the cervical spine to facilitate palpating the cervical spine turbecle. The risk of pneumothorax increases as the dome of the lung is in close proximity to the entry site of the needle. Using fluoroscopic radiological guidance provide a more accurate and safer way of performing the block. A linear cephalad and caudal spread of radio-opaque contrast medium is usually indicative of good needle placement for local anesthetic or neurolytic agent injection (Figure 2).

Interruption of the sympathetic outflow to the head and neck by the stellate ganglion block is substantiated by the presence of Horner's Syndrome: miosis, ptosis and enophthalomos. Other findings such as conjunctival injection, nasal congestion and facial anhydrosis may also be present. (Raj et al, 1996)

The most common side effect of the stellate ganglion block is Horner's Syndrome. Pre-procedural explanation and post-procedural reassurance is necessary and can ease patient’s anxiety. Complication such as seizures can result from intravascular injection. Loss of consciousness, severe hypotension or respiratory compromise can be resulted from subarachnoid injection. Skills of airway management are necessary for the operator of the procedure. Other complications such as brachial plexus block which result in upper extremity motor or sensory deficit, and unilateral phrenic nerve block which result in transient hemidiaphragmatic paresis may also occur. Therefore, bilateral stellate ganglion block is not recommended. Pneumothorax is another potentially life-threatening complication associated with the block, especially with anterior C7 approach. (Waldman et al, 1996, Cousin et al, 1998, Lefkowitz et al, 1996)
Continuous Stellate Ganglion Block

If consistent pain relief is seen with intermittent stellate ganglion blocks, a continuous block should be considered. Catheters can be placed fluoroscopically using the anterior approach at C7. The catheter should be placed close to the lateral portion of the anterior surface of the body of C7 on the affected side. A continuous infusion of 0.1-0.25% bupivicaine or intermittent injections of bupivicaine can be used. There is about a 50% incidence of catheter migration requiring replacement (Linson et al, 1983).

Neurolysis of the Stellate Ganglion

Although anecdotal reports of the use of 1 to 2 ml of 6% aqueous phenol or less than 1.5ml of absolute alcohol in stellate gangliolysis exist with good result and minimal complication, the close proximity of the stellate ganglion to major neurovascular structures makes the injection of neurolytic agents in the area potentially dangerous. Complication such as erosion, thrombosis or spasm of major vessels, cerebral infarction, prolonged hoarseness due to recurrent laryngeal nerve injury and upper limb motor or sensory deficit due to brachial plexus injury may occur. Therefore, the use of the neurolytic stellate block is reserved for exceptional cases after a thorough trial of local anesthetic blockade. Radiological guidance is usually necessary. After evaluating the extent of pain relief with multiple local anesthetic blocks, Arter and Racz describe placement of five mls of a 3% phenol solution (1 ml of triamcinolone, 1.5ml of 0.5% bupivacaine, and 2.5ml of 6% phenol) at the lateral ventral portion of the C7 vertebral body. A series of 150 procedures were performed with no serious complications. Transient Horner’s syndrome did occur with the longest lasting up to 6 months (Arter and Racz, 1990).

Due to the possibility of diffusion of neurolytic solutions (Christie, 1995), stellate RFA may have a significant advantage compared to SGB chemical neurolysis. Radiofrequency lesioning of the stellate ganglion and upper-thoracic sympathetic chain has been described with few complications (Wilkinson, 1984a; Wilkinson, 1984b; Geurts and Stolker, 1993). A radiofrequency cannula is placed under fluoroscopic guidance at the junction of the transverse process and vertebral body of C7. Three lesions are made in a “triangular pattern” after proper negative sensory stimulation to prevent injury to the recurrent laryngeal nerve.
Gasserian Ganglion Block

The trigeminal nerve consists of both motor and sensory fibers. The Gasserian ganglion is formed from two roots that exit the ventral surface of the brain stem at the midpontine level. At the middle cranial fossa, they form a recess called Meckel’s cave, which is formed by an invagination of the surrounding dura mater. The trigeminal cistern, which lies behind the ganglion, contains cerebrospinal fluid. The Gasserian ganglion consists of three sensory divisions, namely, the ophthalmic (V1), maxillary (V2), and mandibular (V3), exiting the anterior convex aspect of the ganglion. The smaller motor root joins the mandibular division and exits the cranial fossa at the foramen ovale. (Brown, 1992)

A gasserian ganglion block is indicated for the palliation of pain due to invasive tumors of the orbit, maxillary sinus, and mandible (Hanowell et al, 1979). Other non-malignant indication includes the management of pain due to trigeminal neuralgia, which has not been responsive to conservative medical management. Oncogenic pain limited to the distribution of the fifth cranial nerve and one of its branches may respond well to radiofrequency or chemical ablation of the involved nerve. When feasible, radiofrequency ablation may be the treatment of choice because analgesia can be achieved without possible sensory loss. The decision of blocking a branch of the fifth cranial nerve versus the Gasserian ganglion relies on the area of pain and likelihood of further tumor invasion. Blocking the Gasserian ganglion may prophylactically extend the field of analgesia in patients with rapid growing malignancy. (Frothingham RE, et al, 1974, Greenberg C, et al, 1969; Lefkowitz, 1996). Siegfried and Broggi reported on the use of neurolysis of the gasserian ganglion with alcohol in 20 cancer patients. 75% obtained initial relief and 60% had relief at 3 months. Of the patients who survived to 12 and 18 months, 70% and 40% had pain relief respectively (Siegfried and Broggi, 1979).

This procedure is usually performed under the guidance of fluoroscopy and intravenous access is required for sedation or management of potential intravascular injections. The patient is placed in the supine position with a shoulder roll in place to maximize cervical extension. By using an oblique caudal-to-cephalic fluoroscopic view, the foramen ovale can usually be identified as an oval-shaped radiolucent area just inferior to the orbit (Figure 3). Having the patient opening the mouth may facilitate the visualization of the foramen ovale. The needle entry site is usually located at the skin just lateral to the second maxillary premolar. Using aseptic technique and after the skin is anesthetized with 1% lidocaine, a 25-gauge, 9-cm Quincke type point spinal needle is advanced aiming towards the medial edge of the foramen ovale until contact is made with the base of the skull. The needle is then withdrawn slightly and advanced laterally into the foramen ovale. Patient should be warned of paresthesia as the needle is advanced into the foramen ovale. The needle should be aspirated for blood. The presence of free flow of cerebrospinal fluid (CSF) may confirm the needle placement. However, the absence of CSF dose not necessary implies incorrect needle positioning for the tip of the needle may reside in the Merkel’s cave, which is more anterior than the trigeminal cistern. (Felstein, 1989) 1 to 2 ml of water-soluble contrast medium may then be injected to confirm the needle placement (Figure 4). For diagnostic block, 0.1 ml aliquots of preservative-free local anesthetic such as 1% lidocaine or 5% bupivacaine may then be injected to a total volume of 0.4 to 0.5 ml. For neurolytic blocks, similar amount of absolute alcohol or 6.5% phenol in glycerin can be used. The destruction of the gasserian ganglion should be reserved for patients who have failed conservative medication interventions. Continuous gasserian ganglion block has been described using a catheter placed in the foramen ovale under fluoroscopic guidance (Raj, 1988).
Local anesthetic can track into the subarachnoid space resulting in brain stem anesthesia. Therefore, the patient should be carefully monitored and life support readily available.

Glossopharyngeal Nerve Block

The glossopharyngeal nerve containing both motor and sensory fibers lies just posterior to the styloïd process of the temporal bone. The motor fibers innervate the stylopharyngeus muscle. The sensory fibers innervate the posterior third of the tongue, the palatine tonsils, and the mucous membranes of the mouth and pharynx. Parasympathetic nerves travel along with the glossopharyngeal nerve to innervate the parotid gland.

A glossopharyngeal nerve block is indicated for the palliation of cancer-related pain in the distribution of glossopharyngeal nerve. Pain in the distribution of the glossopharyngeal nerve can occur in the ear, throat, tongue, or the back of the nose. Swallowing or chewing may often exacerbate pain. Refractory hiccup may also response to glossopharyngeal nerve block. (Babacan A, et al, 1998, Gallacher BP et al, 1997) Percutaneous radiofrequency thermocoagulation of the glossopharyngeal nerve offers low risk and effective pain control. (Shapshay SM et al, 1980)

Extraoral approach

The glossopharyngeal nerve is blocked by first placing the patient in a supine position. Using aseptic technique, a 25-gauge 9 cm Quincke spinal needle is inserted perpendicular to the skin at the mid-point of an imaginary line connecting the mastoid process and the angle of the mandible. Once the needle is in contact with the styloïd process, it is withdrawn and redirected posteriorly until the bony contact is lost. After aspiration for blood and cerebrospinal fluid, 7 to 10 ml of preservative –free local anesthetic is injected in small increments. (Waldman et al, 1996; Bajaj, 1993).

Intraoral approach

With the patient’s mouth open widely, the tongue is retracted inferiorly and contralaterally with a 4X 4 gauze. A 25-gauge, 9-cm long Quicke spinal needle is inserted into the mucosa at the lower lateral portion of the posterior tonsilar pillar. After aspiration for CSF and blood, 7 to
10 ml of preservative free local anesthetic with or without steroid is injected in small increments (Funasaka et al, 1977).

Complications associated with the glossopharyngeal nerve block are the followings: Hematoma, Local anesthetic toxicity, Intravascular injection, Tachycardia, Anesthesia dolorosa, Dysphagia, Infection, Trauma to nerves. Chemical neurolytic blocks should be avoided or reserved for extreme situation because of potential prolonged paralysis of the pharyngeal and laryngeal muscle.

Upper Extremity Overview

The differential diagnosis of upper extremity pain associated with primary or metastatic tumor is extensive (Bonica, 1990). Pain of neuropathic origin may occur from invasion of the cervical or thoracic spinal cord, spinal roots, cervical and brachial plexus (Jaekle, 1991) and individual peripheral nerves (Marmor, 1965). Regional musculoskeletal pain may arise from invasion into the skeletal and soft tissues of the shoulder girdle and upper extremity. Circulatory (arterial, venous or lymphatic) occlusion may cause either ischemic pain or variations of claudication (Gerard et al, 1989). Due to the extensive innervation of the upper extremity by motor and sensory fibers, the benefit of neuroablative procedures for the treatment of pain must be balanced with the potential risks of loss of sensation and motor function. With the generalized neurolysis of agents such as alcohol and phenol, nerves with sensory and motor fibers should not be subjected to chemical neurolysis unless the involved extremity has significantly limited function. Although a majority of cancer patients will “often gratefully exchange unremitting pain for numbness” (Patt, 1993b), patients rarely tolerate loss of motor function even in a non-dominant extremity. As discussed above under neurolysis in the section on the role of regional anesthetic techniques for the treatment of cancer pain, pulsed radiofrequency lesioning is an option that will preserve sensory motor function and should be considered in upper extremity pain.

Sensory innervation of the upper extremity arises from the cervical nerves 5 through 8 and the first thoracic nerve. Innervation to the axilla and upper inner arm is from the lateral branch of the second intercostal nerve (intercostobrachial nerve). Sympathetic innervation derives from the T1 and T2 spinal cord segments. Preganglionic sympathetic axons exit the ventral roots of T1 and T2 and then travel as white communicating rami before joining the sympathetic chain and to synapse at the inferior (stellate), middle, or superior cervical ganglion. Postganglionic nerves either follow the axillary artery to the upper extremity or integrate as the gray communicating rami before joining the brachial plexus to innervate the upper extremity. Use of local anesthetic blocks help to localize the relative contribution of individual nerves to the painful area and subsequent neurolytic blockade can be considered to prolonged pain relief.
Cervical subarachnoid neurolysis

Neurolytic procedures in the cervical spinal cord region have been shown to have limited effectiveness as compared to more caudad levels (Swerdlow, 1984). This is certainly due to multifactorial etiologies such as anatomical factors and multidermatomal involvement of the upper extremity pain. Combined with a higher risk of adverse complication, cervical subarachnoid neurolysis may be considered if limited sensory dermatomal coverage is needed (i.e., a few spinal segments). Since the cervical nerve roots pass horizontally from the cord to their point of exit at the intervertebral foramen, the injection of neurolytic agent is made at the spinal segment level to be blocked (Figure 5) (Swerdlow, 1993).

Intrathecal alcohol

The patient is placed in the lateral position with the affected extremity upward. The patient should be rolled forward into a 45° oblique position. This will maintain the posterior roots in the uppermost position. A spinal needle should then be placed into the intrathecal space at the vertebral interspace of the dermatome to be blocked. A volume of up to 0.5ml of 100% alcohol may be administered at a slow rate. It is recommended that a tuberculin syringe is used and increments of 0.1ml are administered every minute. The patient may experience a transient burning sensation in the dermatomal segments to be blocked. If 0.5 ml has been reached and the painful dermatomal segments have not been blocked, then a second needle may be placed 2 spinal segments above or below the first needle placement with the same dosing procedures followed. On completion of the injection, the patient should remain in the same position for 15 to 20 minutes after which the CSF alcohol concentrations are negligible precluding any further extension of the block (Figure 6) (Swerdlow, 1993).
Bilateral blocks may be achieved with the patient in the prone position with the posterior roots uppermost. In this position, the injected alcohol will spread bilaterally to both posterior roots. Alternatively, each side can be done separately as described below.

**Intrathecal phenol**

The patient is placed in the lateral position with the affected extremity downward. The patient should be rolled backward into a 45° oblique position. This will maintain the posterior roots in the lowermost position. A spinal needle should then be placed into the intrathecal space at the vertebral interspace of the dermatome to be blocked. A volume of up to 0.5ml of 5 - 10% phenol may be administered at a slow rate. It is recommended that a tuberculin syringe is used and increments of 0.1ml are administered every minute. Since phenol has local anesthetic properties, the patient should experience a feeling of warmth and tingling in the affected dermatome. If these symptoms do not occur, it has been suggested that higher concentrations should be used (Ichianagi et al, 1975). If 0.5 ml has been reached and the painful dermatomal segments have not been blocked, then a second needle may be placed 2 spinal segments above or below the first needle placement with the same dosing procedures followed. On completion of the injection, the patient should remain in the same position for 15 to 20 minutes after which the CSF phenol concentrations are negligible precluding any further extension of the block (Figure 7) (Swerdlow, 1993).
Cervical epidural neurolysis

There is limited experience in cervical epidural neurolysis. Racz reported on a series of 18 patients with cancer pain who were treated with cervical epidural phenol. Six patients had pain relief on discharge and 5 patients had pain relief lasting from 1 to 3 months (Racz, 1977). Korevaar’s experience in upper thoracic neurolysis using alcohol through an indwelling catheter showed some promise, but extensive utilization has not been realized (Korevaar, 1990).

Technique

An epidural catheter is placed at the C7-T1 interspace and advanced to the desired level using fluoroscopic guidance. Catheter placement can be verified by either injection of contrast or local anesthetic. If local anesthetics are used, the volume of phenol used is equal to the required volume of local anesthetic required for pain relief. However, before administering the phenol, the local anesthetic block should be allowed to fully regress to avoid spread of the phenol block beyond the initial local anesthetic test block. Phenol concentrations vary from 5-10% (Cousins, 1988).

Paravertebral Block and Neurolysis

Due to the extensive sensory overlap of the upper extremity, paravertebral somatic blocks are usually reserved for well-localized pain. Even with localization, multiple cervical nerve roots are required to be blocked, usually resulting in some degree of motor weakness. In a case report by Kaplan et al, residual pain after a phenol neurolytic procedure of the brachial plexus was managed with paravertebral phenol blocks. Using 0.5-1.0 mls of 6% aqueous phenol per segment, injections at C5 and C6 and later in response to tumor enlargement, at T1-T3, provided supplemental relief of upper extremity pain secondary to a sarcoma of the humeral head (Kaplan, 1988). Radiologic guidance is strongly recommended for neurolytic paravertebral block, as well as careful observation of the effects of local anesthetic test dose(s).
used in diagnostic procedures prior to neurolytic injection. The administration of small doses of neurolytic solutions is recommended to minimize the risk of subarachnoid or epidural spread.

Brachial Plexus Block and Neurolysis

Intermittent brachial plexus blockade can result in short term pain relief and give patients respite from severe pain. Continuous interscalene infusions of local anesthetic has been shown to be effective in symptomatic treatment of cancer pain for up to two weeks (Sato, 1994). A supraclavicular approach utilizing nerve stimulation at the level of C6 in the interscalene groove has been described most recently by Haasio et al and has an advantage of improved proximal upper extremity coverage (Haasio, 1997). The infraclavicular technique is reviewed and described by Raj, which has improved distal upper extremity coverage, including the ulnar segment of the medial cord, and the intercostobrachial nerve (Raj, 1997). While neither of these techniques was described for the use in cancer pain management, their effectiveness may prove efficacious in the treatment of proximal or distal upper extremity pain secondary to tumor invasion.

Tumor encroachment is one of the most common causes of brachial plexopathy (Kori, 1981). A significant percentage of these tumors arise as breast cancer, lymphoma and apical tumors of the lung (Pancoast tumor). Pain is ubiquitous in these patients with the lower trunk (C7-T1) most often involved. Due to the mixed sensory and motor components of the brachial plexus, neurolysis should not be performed unless the upper extremity is already weak or useless secondary to pain or a physiologic derangement. Multiple case reports (Bonica, 1990b; Kaplan, 1988) have described approaches to infiltrate neurolytic solutions around the brachial plexus. Bonica describes, after two local anesthetic prognostic blocks, using 25mls of 5% aqueous phenol with effective pain relief, and weakness, and 20mls of 95% alcohol with effective pain relief and paralysis. Kaplan reported a case of a supraclavicular brachial plexus injection of 12.5 mls of 6% phenol in water with significant but incomplete relief. Patt (Patt, 1993) describes using 10-20 mls of 10-20% aqueous phenol mixed with 20% glycerin injected via an axillary approach with good to excellent pain relief from tumor invasion of the brachial plexus. There were no unexpected complications, but increased motor weakness occurred in all cases. The duration of the pain relief from these case reports ranged from weeks to months, and occasionally required repeat injections.

Intermittent interscalene neurolysis has been performed for tumors of the upper extremity via the interscalene approach. Case reports by Mullin and Neill discussed using 3% phenol and 50% alcohol respectively with minimal neurological sequelae (Mullin, 1980; Neill, 1979).

Peripheral Nerve Blocks and Neurolysis

A good understanding of the sensory innervation to the upper extremity can be very helpful in guiding neural blockade for pain control. If the pain distribution is limited to one or two peripheral nerves, then neurolytic techniques may result in long-term pain relief in selected patients. Suprascapular chemical neurolysis has been utilized for shoulder and upper extremity pain (Patt, 1993) Using localization with nerve stimulation, an injection of 4-5 mls of 10% phenol and 4 mls of 95% alcohol afforded weeks of pain relief and no loss of motor function.
Cryoneuroablation of the suprascalpular nerve is minimally invasive and has been used as an effective treatment for chronic pain of the shoulder. This procedure also may provide prolonged relief of pain of the upper shoulder secondary to multiple myeloma, lung cancer etc. For the procedure, the patient is placed in the prone position, and a 14 or 12 gauge intravenous catheter is advanced into the supraspinatus notch, parallel to the direction of the nerve. The 1.4 or 2.0 mm cryoprobe is advanced until the nerve is localized using the sensory stimulation. Usually two to three 3-minute freeze cycles are adequate.

Stellate Ganglion Blockade and Neurolysis

Stellate ganglion block (SGB) may be effective for upper extremity pain associated with visceral involvement, brachialgia or certain types of deafferentation processes (secondary to radiation therapy). Local anesthetic SGB have been utilized and shown to have some long lasting effect in lung cancer patients. For a further discussion on stellate ganglion blockade and neurolysis, refer to section under head and neck.

Cervical Epidural Infusions

For upper extremity pain that does not respond to intermittent regional anesthetic techniques, a continuous cervical epidural should be considered. A cervical epidural infusion can be accomplished with a percutaneous temporary catheter with the infusion of low concentrations of bupivacaine (1/32% - 1/10%). The tip of the catheter should be placed as close as possible to the dermatomes supplying the brachial plexus (C5-T1). For a discussion on cervical epidural infusions, refer to section on head and neck.

Thoracic and Abdominal Wall.
Overview

The etiology of pain originating in the chest and abdominal wall varies, but usually is secondary to neoplastic invasion of the vertebral bodies and rib cage (prostate, breast), spinal cord and peripheral nerves, parietal peritoneum (lung). (Colemen 1997, Osborn et al, 1995). Various treatments of the thoracic or abdominal wall pain syndromes are derived in part from regional anesthetic procedures such as treated with intercostal (Churcher, 1989; Moore and Bridenbaugh, 1962; Moore, 1984) or paravertebral blocks (Vernon, 1930), and the quest for a longer duration of pain relief with the use of various techniques such as intercostal neurolysis, epidural and subarachnoid neurolysis.

Intercostal Nerve Blocks and Neurolysis

An intercostal nerve block is usually performed posteriorly at the angle of the rib just lateral to the paraspinous muscles where the ribs are usually easily palpable (Thompson, 1996). The nerve is still contained within the intercostal groove where drug tends to be spread more predictably (Moore, 1984), and failures may be less than with anterior approaches because the nerve has not yet given off its lateral cutaneous branch near the midaxillary line. (Cousins and Bridenbaugh, 1988) The use of radiologic guidance has been cited for intercostal nerve block (Moore, 1984) and should be used especially when neurolysis is attempted. “Walking the needle” toward the inferior margin and under the rib (2-4 mm), with a concomitant paresthesia, are reliable confirmations of needle placement (Figure 8). The most significant complication of an intercostal nerve block is pneumothorax, although with proper technique the incidence of symptomatic pneumothorax may be as low as 0.092%, as was demonstrated in a series of 50,097
intercostal blocks performed (Moore and Bridenbaugh, 1962). The requirement for chest tube drainage is rare and should be considered only if the lung fails to expand after observation or percutaneous aspiration fails to relieve the pneumothorax. Previous surgical procedures of the chest (partial or complete lung resection) increase the risk of complications from intercostal nerve blocks and ablative procedures. A case report by Atkinson et al highlights a patient with adhesions who experienced acute bronchospasm following a presumed intra-bronchial or intra-pulmonary injection of 0.5 ml of 8% phenol in saline (Atkinson, 1989).

The reports on treatment of thoracic and abdominal wall pain syndromes with intercostal neurolysis are sparse. Chemical neurolysis was reported by Doyle with a series of 46 hospice patients treated with multiple intercostal blocks utilizing 1.0 to 1.5 ml of 5% phenol “in oil” per segment. Total relief of pain for a mean duration of 3 weeks (range 1 to 6 weeks) was achieved and no complications were reported. (Doyle, 1982). Intercostal cryo-neurolysis has been used in the treatment of post-thoracotomy pain (Pastor et al, 1996) with a variable duration of relief. In patients with intercostal neuralgia after thoracotomy (91%) and Herpes Zoster (9%), Green reported on percutaneous using a large probe through a 14-gauge cannula for a single cycle of four minutes (Green et al, 1993). All patients experienced initial pain relief, which regressed over 2 to 3 weeks and ultimately, one-half and one-quarter of patients reported significant pain relief at 3 and 6 months, respectively. Radiofrequency lesioning of peripheral nerves is discouraged, due to the development of severe neuritis and creation of deafferentation syndrome. With the advent of pulsed radio-frequency (PRF) generators, case reports of treatment of some forms of neuropathic pain syndromes may signal an improved method of radiofrequency ablation of intercostal DRG, or peripheral nerves. The reported advantage of PRF is there is no clinical evidence of neural damage due to the minimal elevation of probe temperature to 42°C. (Munglani, 1999). For a discussion of pulse radiofrequency lesioning, refer above to neurolysis in the section on the role of regional anesthetic techniques for the treatment of cancer pain.

Paravertebral Blocks and Neurolysis
Paravertebral neurolytic blocks of the somatic roots just outside the intervertebral foramina are frequently undertaken (Thompson and Moore, 1988). Bonica (Bonica, 1954) mentions favorable results subsequent to the paravertebral injection of 1 ml alcohol per involved segment in patients with abdominal and chest wall pain secondary to vertebral, paravertebral, and visceral neoplasms
associated with peritoneal invasion. Jain mentions performed 39 paravertebral alcohol and phenol injections under radiologic guidance without serious complications (Jain, 1990). In a brief report, Vernon noted good relief of back pain of metastatic origin and no untoward effects after paravertebral injection of alcohol in two patients (Vernon, 1930). The usual technique, which relies on paresthesias and bony landmarks such as the transverse process, radiological guidance, careful observation of the effects of preneurolytic test doses of local anesthetic, and fractionated administration to avoid subarachnoid, epidural, or intrapleural spread, all of which have been documented (Conacher and Korkri, 1987), are indicated.

Radio-frequency lesioning of thoracic intercostal nerves by percutaneous partial rhizotomy has been well documented (Stolker et al, 1994). More recently, radio-frequency ablation of the thoracic dorsal root ganglion was shown to be effective in 52% of patients with limited segmental non-malignant thoracic pain. The thoracic dorsal root ganglion is located in the superior dorsal quadrant of the foramen. In the lower thoracic vertebra, the percutaneous access is approached laterally and directed medially toward the vertebral body. In the upper thoracic region, a small laminotomy is created directly over the superior aspect of the foramina. Van Kleef et al treated 43 patients utilizing a RF probe adjacent to the 67C for 60sec and noted no major complications, such as dysesthesia or increased pain (van Kleef et al, 1995). Although three cases of pneumothorax occurred, no patients experienced post-treatment neuritis. Munglani provides a case report of PRF ablation of the spinal roots of T2-T4 created significant relief of neuropathic pain of the anterior chest wall secondary to and radiation, without loss of sensation (Munglani, 1999).

**Thoracic Sympathectomy**

Thoracic sympathetic block has been indicated for intractable cancer pain of the upper two-thirds of the esophagus (T2-T8) and pleuritic chest pain secondary to lung neoplasm. (Bonica, 1990). The difficulty of multiple needle placements, potential serious complications and the effectiveness of epidural and subarachnoid neurolysis have minimized the usefulness of this procedure. Permanent sympathectomy may be accomplished with radiofrequency lesioning (Figure 9) (Kline, 1996).

**Interpleural Analgesia and Neurolysis**

Placement of an interpleural catheter for treatment of cancer pain has been used sparingly secondary to the concerns of local anesthetic absorption, (especially bupivacaine) and the risk of pneumothorax (O’Leary and Myers, 1997) in patients with marginal pulmonary function (Figure 10) (Myers et al, 1996). O’Leary and Myers described the use in ten patients with metastatic disease to the chest, neck and upper extremities using various infusions of bupivacaine up to 0.5% (O’Leary and Myers, 1997). Neurolytic interpleural therapy was reported by Lema et el for
a patient with metastatic esophageal cancer (Lema et al, 1992). The infusion of 6% phenol provided significant reduction of chest pain and opioid requirement over a four-week period, without histiologic pleura or lung damage.

Thoracic Subarachnoid and Epidural Neurolysis

The upper and lower thoracic regions provide relative safe and simple access for the performance of subarachnoid chemical neurolysis utilizing either phenol or alcohol. The possible advantages of subarachnoid block in this region include low morbidity, the presence of a reliable end point using cerebral spinal fluid, no requirement to localize multiple individual nerves, and fewer problems related to overlapping distribution. While the chance of pneumothorax exists, the probability is limited. Epidural chemical neurolysis has been utilized using single or multiple injections via an epidural catheter. (see cervical epidural neurolysis (Korevaar, 1990). The upper thoracic nerve roots pass horizontally from the cord to their point of exit at the intervertebral foramen whereas in the mid and lower thoracic region, the nerve root passes out of the vertebral column at 1-2 segments below the exit from the spinal cord. Since it is thought that the neurolytic agent exerts its maximum effect on the fine rootlets leaving the cord, the needle entry site should be 1-2 segments above the vertebral column exit site of the nerve root (Figure 5).

Intrathecal alcohol

The patient is placed in the lateral position with the affected extremity upward. The patient should be rolled forward into a 45° oblique position. This will maintain the posterior roots in the uppermost position. For upper thoracic pain, a spinal needle is placed into the intrathecal space at the vertebral interspace of the dermatome to be blocked. For mid to lower thoracic or abdominal pain, a spinal needle is placed into the intrathecal space 1-2 segments above the vertebral interspace of the dermatome to be blocked. A volume of up to 1.0 ml of
100% alcohol may be administered at a slow rate. It is recommended that a tuberculin syringe is used and increments of 0.2ml are administered every minute. The patient may experience a transient burning sensation in the dermatomal segments to be blocked. If 1.0 ml has been reached and the painful dermatomal segments have not been blocked, then a second needle may be placed 2 spinal segments above or below the first needle placement with the same dosing procedures followed. On completion of the injection, the patient should remain in the same position for 15 to 20 minutes after which the CSF alcohol concentrations are negligible precluding any further extension of the block (Figure 6).

Bilateral blocks may be achieved with the patient in the prone position with the posterior roots uppermost. In this position, the injected alcohol will spread bilaterally to both posterior roots. Alternatively, each side can be done separately as described below.

**Intrathecal phenol**

The patient is placed in the lateral position with the affected extremity downward. The patient should be rolled backward into a 45° oblique position. This will maintain the posterior roots in the lower most position. For upper thoracic pain, a spinal needle is placed into the intrathecal space at the vertebral interspace of the dermatome to be blocked. For mid to lower thoracic or abdominal pain, a spinal needle is placed into the intrathecal space 1-2 segments above the vertebral interspace of the dermatome to be blocked. A volume of up to 1.0 ml of 5 - 10% phenol may be administered at a slow rate. It is recommended that a tuberculin syringe is used and increments of 0.2 ml are administered every minute. Since phenol has local anesthetic properties, the patient should experience a feeling of warmth and tingling in the affected dermatome. If these symptoms do not occur, it has been suggested that higher concentrations should be used (Ichiyanagi et al). If 1.0 ml has been reached and the painful dermatomal segments have not been blocked, then a second needle may be placed 2 spinal segments above or below the first needle placement with the same dosing procedures followed. On completion of the injection, the patient should remain in the same position for 15 to 20 minutes after which the CSF phenol concentrations are negligible precluding any further extension of the block (Figure 7).

**Abdominal Pain**

**Overview**

The upper GI tract and surrounding viscera receive sensory innervation from T5-T12 which travels through the celiac plexus. Therefore, blockade of the celiac plexus will denervate sensation to the upper GI tract (liver, stomach, pancreas, spleen, kidneys) and is commonly used for painful disease of these structures (Patt, et al, 1998; de Leon-Casasola et al, 2000). The celiac plexus receives input from the greater (T5-T10), lesser (T10-T11) and least (T12) splanchnic nerve. The aorta is just posterior to the plexus on the left.

Local anesthetic block of the celiac plexus will result in transient pain relief and a neurolytic block is usually required for long-term pain relief. Whereas somatic neurolytic blocks may result in sensory motor dysfunction, this is a rare occurrence with a celiac plexus block making it a very attractive technique, which should be used early in patients unresponsive to conservative measures. Although neurolytic celiac plexus blocks are most often used for the treatment of pancreatic cancer pain, studies have shown similar results with nonpancreatic cancer pain (70 – 90% satisfactory pain relief at death) (Brown, 1989; Sharfman and Walsh, 1990; Eisenberg et al, 1995).
Celiac Plexus Block and Neurolysis

The celiac plexus can be blocked by either anterior or posterior approaches. Posterior approach includes retrocrural, anterocrural, transaortic, and splanchnicectomy techniques. A prospective randomized study in 61 pancreatic cancer patients showed no significant differences in outcomes between the retrocrural, transaortic and splanchnicectomy techniques (Ischia et al, 1983). In the retrocrural technique, local anesthetic or neurolytic agent is injected posterior and cephalic to the diaphragmatic crura, whereas in the anterocrural approach, the blocking agent is injected anterior to the diaphragmatic crura behind the aorta at the level of L1 vertebra. Both the anterocrural and retrocrural techniques can be performed with the patients lying in prone position under fluoroscopic or CT guidance. The anterior approach is usually performed with patients in supine position under the guidance of CT scan.

Retrocrural approach

The patient is positioned in the prone position with a pillow underneath the abdomen to decrease lumbar lordosis. The inferior borders of the tip of the twelfth ribs are marked as the needle entry site. The skin is prepared with aseptic technique and sites of needle entry are anesthetized with local anesthetic. Under an anteroposterior fluoroscopic view, a 22-Gauge 15cm long needle is advanced from the needle entry site towards the inferior one third of the L1 vertebral body. Once the needle is contact with the vertebral column, 2 to 3 ml of local anesthetic should be given to facilitate needle manipulation along the vertebral body. The needle is then withdrawn to subcutaneous tissue and advanced with a steepened angle. The maneuver is repeated until the needle slips off the L1 vertebral body. Under a lateral fluoroscopic view, the needle is then advanced to the anterior border of the L1 vertebral body. The tip of the needle is advanced 2 cm on the right and preferably 1 cm on the left until the aortic pulsations are felt. After removing the stylets of the needles, the operator should inspect the hubs of the needles for blood, cerebrospinal fluid and urine. Then 2 to 3 mL of water-soluble contrast medium is injected. Ideally, contrast medium should spread along the anterior border of the vertebral column with a smooth posterior contour that corresponds to the psoas fascia on the lateral fluoroscopic view. (Figure 11A and 11B) On the anteroposterior view, the dye spread should be just slightly off the midline and concentrated near the L1 vertebral body. After aspiration, 2 ml of local anesthetic is injected as a test dose at each needle to rule out intravascular or intrathecal injection. Then 10 to 15 ml of local anesthetic is injected at each needle. For diagnostic blocks 2 % lidocaine or 0.25 % bupivacaine can be used. Neurolytic agents such as anhydrous alcohol or 6 % phenol (total of 30 to 40 ml) can be used only after positive response has been established with local anesthetic injection. Injection of alcohol can cause severe pain; therefore, injection of 10 to 20 ml of local anesthetic such as 0.25% bupivacaine prior to the neurolytic agent can minimized discomfort associated with the neurolytic agent (de Leon-Casasola et al, 2000).
Anterocrural approach

This approach is similar to the retrocrural approach, except the needle entry sites are closer to the midline than the latter. The needle tips will be anterior and inferior to the diaphragm, and thus smaller volumes of local anesthetic and neurolytic agents are needed with an equal or better efficacy than the retrocrural approach (Lopez, 1987).

Transaortic Approach

This unilateral left-sided needle placement technique was described by Ischia et al. (1983). Using a similar posterior approach as described in the classical posterior retrocrural approach, the needle is walked off the L1 vertebral body and advanced until tip is in the preaortic connective tissue which generally felt as an increase of resistance and pulsatile sensation. The needle is then advanced through the posterior aortic wall, the lumen and the anterior aortic wall. Beyond that point, a new loss of resistance will be felt and the tip of the needle is in the preaortic area where the celiac plexus is located. Alternatively, applying constant negative aspiration pressure via a 5 ml syringe can facilitate needle placement. A sudden loss of aspiration pressure after the needle has passed through the vessel wall will signify the tip of the needle is in close proximity of the plexus. The needle placement is further confirmed with contrast medium. (Feldstein GS et al, 1986)

Splanchnicectomy

This is a bilateral block is similar to the technique described for the retrocrural approach however, the needle is directed to the upper border of T12. The lateral view should show the needle tips approximately 0.5 cm anterior to the middle to upper body of T12. Anteroposterior view should show the needle tips approximately 0.5 – 1.0 cm inside the lateral edge of T12. This compartment is bound anteriorly by the major vessels, posteriorly by the vertebral body, laterally by the parietal pleura and inferiorly by the crus of the diaphragm (Moore, 1967).

Anterior Approach

This approach is performed with the patient in supine position under CT scan guidance. The greatest advantage of this technique is that for patients with abdominal pain or colostomies, the supine position is more comfortable than prone position. In addition, this approach only requires one needle placement, which further minimizes discomfort associated with the injection.
The precrural needle placement also decreases the risk of neurological injury associated with retrocrural spread of drugs to the somatic nerves, epidural or subarachnoid space. However, potential risk associated with this approach does include infection, abscess, and hemorrhage and fistula formation. Patient preparation is similar to the posterior approaches. Prophylactic intravenous antibiotic is recommended to decrease the risk of infection.

First, the patient is placed on a CT table and the abdomen is prepared with aseptic technique. The needle entry site is marked approximately 1 to 1.5 cm below and to the left of the xiphoid process. A 22-gauge, 15cm needle is introduced perpendicular to the skin at the anesthetized area and advanced to the depth of the anterior wall of the aorta as estimated by the CT scan. Final needle placement is confirmed with CT imaging. 15 to 20 ml of local anesthetics such as 2% lidocaine or .25% bupivacaine injected in small increments is sufficient for diagnostic block. For neurolytic blockade, 20 mL of anhydrous alcohol has been used with good result.

Complication

Risks of a celiac plexus block, regardless of technique, include hypotension, neurologic injury, local anesthetic toxicity, hematoma, and diarrhea. Hypotension occurs because of loss of sympathetic tone to the viscera resulting pooling of blood in the viscera. Over 2-3 days, this hypotension resolves with fluid shifts. Neurological injury can occur since the needle is advanced through the upper lumbar plexus. If the major vessels are entered, local anesthetic toxicity or hematoma can develop. Since the sympathetic supply to the abdominal visceral is removed, there is an unopposed parasympathetic innervation, which can result in diarrhea. However, this usually resolves over 2-3 days. With the splanchnicectomy, a pneumothorax may occur and it is important to keep the needle as close as possible to the vertebral body.

Pelvic Pain

Overview

The superior hypogastric plexus lies in the retroperitoneal space, just below the aortic bifurcation, anterior to the fifth lumbar vertebra and the first sacral vertebral body. The confluence of branches from the lumbar sympathetic chain (lumbar splanchnics) and branches of the aortic plexus form the plexus. It also receives parasympathetic contribution from the S2-S4 ventral roots. The superior hypogastric plexus divides into the right and left hypogastric nerves, which descend lateral to the sigmoid colon and rectosigmoid junction into the inferior hypogastric plexus. The hypogastric plexus, which contains afferent pain fibers and postganglionic sympathetic fibers as well as preganglionic parasympathetic fibers, innervate pelvic viscera. (Cousin et al,1998). Unlike the celiac plexus, the superior hypogastric plexus is in close proximity to the sacral plexus; therefore, there is a greater risk of somatic block resulting.

The first published study on the superior hypogastric plexus block was by Plancarte et al who performed this procedure on 28 patients with pelvic cancer related pain (20 cervical cancer, 4 prostate cancer, 1 testicular cancer and 3 radiation enteritis). There was an overall 70% reduction in pain and no complications (Plancarte et al, 1990). In 1993, de Leon-Casasola et al showed similar results in 26 patients with pelvic cancer related pain (de Leon-Casasola et al, 1993a).
Superior Hypogastric Plexus Block and Neurolysis

Place the patient in prone position with a pillow under the pelvic area to decrease lumbar lordosis. Clean the lumbosacral area with aseptic technique. Using fluoroscopic imaging, identify the L4-5 interspinous space on the AP view. The needle entry site will be marked 5 to 7 cm lateral to the midpoint of the L4-5 interspinous space. Skin wheal is given with local anesthesia at the needle entry site. Under the guidance of fluoroscopy, direct a 22-gauge 15-cm needle at approximately 30 to 45 degrees medially and caudally towards the anterolateral surface of the L5 vertebral body. Adjust the angle of the needle until it has walked off the vertebral body. If the L5 transverse process is encountered, the needle is withdrawn to the subcutaneous tissue and redirected caudally with a steeper angle. If the needle still cannot pass the iliac crest and L5 transverse process, a slight bend of the needle to create a curvature may facilitate the needle placement. Alternatively, passing the needle through the L5-S1 under biplanar view or using computed tomography (CT) has been reported as safe and successful ways of blocking the superior hypogastric plexus. Once the tip of the needle is at the anterolateral border of the vertebral body, 2 to 3 ml of water-soluble contrast medium can be injected to confirm the needle placement. A smooth contour of the contrast medium along the anterior vertebral border on the lateral view and paramedian or median dye spread on the AP view will reassure the needle placement. Due to the presence of the bifurcation of the common iliac vessels, cautious aspiration the use of test dose of injection solution is recommended. For diagnostic blocks, 8 ml of .25% bupivacaine or 1% lidocaine is injected through each needle, and for neurolysis, 8 ml of 6 to 10% aqueous phenol or anhydrous alcohol is used. (Planarte et al, 1990, 1997) The use of computed tomography has also been described for this procedure (de LeoCasasola et al, 1993).

With the close proximity of the sacral plexus, smaller volumes of local anesthetic or neurolytic agents should be used (5-8 ml) than the celiac plexus block (20-40 ml). This will avoid spillage of the agent onto the sacral plexus and somatic blockade. Other complications include vascular puncture with local anesthetic toxicity or hematoma formation.

Lower Extremity

Overview

The differential diagnosis of lower extremity pain associated with primary or metastatic tumor is extensive (Jaekle et al, 1985; Pettigrew et al, 1984). Pain of neuropathic origin may result from invasion of the spinal cord, spinal roots, lumbar and sacral plexus and individual peripheral nerves (Patchell and Posner, 1985; Posner, 1987). Regional musculoskeletal pain may arise from invasion into the skeletal and soft tissues of the pelvic girdle and lower extremity. Circulatory (arterial, venous or lymphatic) occlusion may cause either ischemic pain or variations of claudication (Gerard et al, 1989). Due to the extensive innervation of the lower extremity by motor and sensory fibers, the benefit of neuroablative procedures for the treatment of pain must be balanced with the potential risks of loss of sensation and motor function. With the generalized neurolysis of agents such as alcohol and phenol, nerves with sensory and motor fibers should not be subjected to chemical neurolysis unless the involved extremity has significantly limited function. The negative effects of motor dysfunction of the lower extremity should be weighed with the positive effects of pain relief. As discussed above under neurolysis in the section on the role of regional anesthetic techniques for the treatment of cancer pain, pulsed radiofrequency lesioning is an option that will preserve sensory motor function and should be considered in lower extremity pain.
Sensory innervation of the lower extremity arises from the lumbar plexus (L1 – L4) and the sacral plexus (L5-S3). Sympathetic innervation derives from the L1 and L2 spinal cord segments. Preganglionic sympathetic axons exit the ventral roots of L1 and L2 and then travel as white communicating rami before joining the sympathetic chain and to synapse at the lumbar ganglion. Postganglionic nerves either follow the femoral artery to the lower extremity or integrate as the gray communicating rami before joining the lumbosacral plexus to innervate the lower extremity. Use of local anesthetic blocks help to localize the relative contribution of individual nerves to the painful area and subsequent neurolytic blockade can be considered to prolonged pain relief.

Lumbar subarachnoid neurolysis

Subarachnoid neurolysis of the lumbar region may be considered if limited sensory dermatomal coverage is needed (i.e. a few spinal segments). The lumbar nerve roots are located at the T11-T12 level and the sacral nerve roots are located at the L1-L2 level. Therefore, for lumbar and sacral dermatomes, neurolysis should be performed at the T11-T12 and L1-L2 interspace, respectively (Figure 5).

Intrathecal alcohol

The patient is placed in the lateral position with the affected extremity upward. The patient should be rolled forward into a 45° oblique position. This will maintain the posterior roots in the uppermost position. A spinal needle should then be placed into the intrathecal space at the T11-T12 interspace for lumbar dermatomes and the L1-L2 interspace for sacral dermatomes. A volume of up to 1.0 ml of 100% alcohol may be administered at a slow rate. It is recommended that a tuberculin syringe is used and increments of 0.2 ml are administered every minute. The patient may experience a transient burning sensation in the dermatomal segments to be blocked. If 1.0 ml has been reached and the painful dermatomal segments have not been blocked, then a second needle may be placed 2 spinal segments above or below the first needle placement with the same dosing procedures followed. On completion of the injection, the patient should remain in the same position for 15 to 20 minutes after which the CSF alcohol concentrations are negligible precluding any further extension of the block (Figure 6).

Bilateral blocks may be achieved with the patient in the prone position with the posterior roots uppermost. In this position, the injected alcohol will spread bilaterally to both posterior roots. Alternatively, each side can be done separately as described below.

Intrathecal phenol

The patient is placed in the lateral position with the affected extremity downward. The patient should be rolled backward into a 45° oblique position. This will maintain the posterior roots in the lowermost position. A spinal needle should then be placed into the intrathecal space at the T11-T12 interspace for lumbar dermatomes and the L1-L2 interspace for sacral dermatomes. A volume of up to 1.0 ml of 5 - 10% phenol may be administered at a slow rate. It is recommended that a tuberculin syringe is used and increments of 1.0 ml are administered every minute. Since phenol has local anesthetic properties, the patient should experience a feeling of warmth and tingling in the affected dermatome. If these symptoms do not occur, it has been suggested that higher concentrations should be used (Ichiyanagi et al, 1975). If 1.0 ml has
been reached and the painful dermatomal segments have not been blocked, then a second needle may be placed 2 spinal segments above or below the first needle placement with the same dosing procedures followed. On completion of the injection, the patient should remain in the same position for 15 to 20 minutes after which the CSF phenol concentrations are negligible precluding any further extension of the block (Figure 7).

**Lumbar epidural neurolysis**

There is limited experience in lumbar epidural neurolysis. There are anecdotal reports of satisfactory pain relief with lumbar and caudal epidural neurolysis with phenol; however, there is no data available. The technique is similar as described for the cervical region above (Racz et al, 1977).

**Paravertebral Block and Neurolysis**

Due to the extensive sensory overlap of the lower extremity, paravertebral somatic blocks are usually reserved for well-localized pain. Even with localization, multiple lumbar nerve roots are required to be blocked, usually resulting in some degree of motor weakness. Radiological guidance is strongly recommended for neurolytic paravertebral block, as well as careful observation of the effects of local anesthetic test dose(s) used in diagnostic procedures prior to neurolytic injection. The administration of small doses of neurolytic solutions is recommended to minimize the risk of subarachnoid or epidural spread.

**Technique**

Place the patient in prone position with a pillow under the pelvic area to decrease lumbar lordosis. Clean the lumbosacral area with aseptic technique. Using fluoroscopic imaging, identify the transverse process of the vertebral level to be blocked. The needle entry site will be approximately 2 cm below the lateral edge of the vertebral process. Skin wheal is given with local anesthesia at the needle entry site. Under the guidance of fluoroscopy, direct a 22-gauge 3.5 inch needle with a 1 cm 45° angled tip at approximately 30 to 45 degrees medially and cephalad towards the junction of the transverse process with the vertebral body. This direction will avoid contact with the nerve root. Alternatively, an oblique view with fluoroscopy can be used to view the neural foramen and guide the angle of needle entry. The curved tip can be used to guide the direction of the needle advancement by twisting the needle. Once the neural foramen is approached, the needle should be rotated so that the curve tip enters the foramen. Injection of contrast should spread into the neural foramen along the nerve root. If the needle is advanced far enough into the foramen, epidural spread will result. Alternatively, an 18-gauge 3.5 inch Crawford needle can be used. If injected dye does not enter the neural foramen, a 5 inch 22-gauge spinal needle can then be advanced through the Crawford needle into the foramen. (Figure 12A and 12B).
Lumbar Plexus Block and Neurolysis

Intermittent lumbar plexus blockade can result in short term pain relief and give patients respite from severe pain. Continuous lumbar plexus infusions of local anesthetic through a catheter placed in the psoas compartment may be beneficial. There is minimal data on lumbar plexus neurolysis. Calava et al reported on a 56-year-old patient with severe lower extremity pain after amputation. The pain was refractory to epidural local anesthetic and opioid infusions. 10 cc of 10% phenol injected into the psoas sheath resulted in a significant reduction in pain with no evidence of motor blockade (Calava, 1996).

Peripheral Neurolysis

Tibial phenol neurolysis and cryoablation has been utilized for lower extremity cancer pain (Ramamurthy et al, 1985). The techniques described above for the upper extremity can also be applied for the lower extremity.

Lumbar Sympathetic Ganglion Blockade and Neurolysis

There are many indications for the use of a lumbar sympathetic ganglion block (LSB) for the treatment of lower cancer pain. These include pain resulting from herpes zoster, postherpetic neuralgia (Currey and Dalsania, 1991), lumbar vertebral metastasis, neuropathic pain secondary to chemotherapy or radiation therapy, pain from central nervous system lesions, and complex regional pain syndrome type I and type II (Arden et al, 1998). Response to LSB with local anesthetic can serve as a diagnostic indication that pain transmission can be due to autonomic contribution. In addition, the initial response to the block will also serve as a prognostic indicator for possible repeated local anesthetic blocks, neurolytic block, or surgical intervention.

Technique

The lumbar sympathetic ganglions are located at the anterolateral edge of the vertebral body just anterior and medial to the psoas muscle. Since ganglion at L3 and below do not receive white rami, the block can be performed at the L2 ganglion which will adequately block the sympathetic supply to the lower extremity. The block is performed with the patient in the prone position. The needle entry site is approximately 5-8 cm lateral to the spinous process of L2. Using a 5-8 inch 22 gauge needle, the needle is directed medially at approximately a 45-degree angle until contact is made on the vertebral body of L2. The needle is then withdrawn.
and the angle increased until the needle slides off the anterolateral edge of L2. A loss of resistance technique to air may be used since there is a nice loss of resistance as the needle passes out of the psoas muscle. The tip of the needle should be located on the anterolateral edge of the L2 vertebral body and dye should demonstrate a caudad and cephalad spread. If the dye outlines the fibers of the psoas muscle, the needle should be advanced further. 15cc of local anesthetic or 6-10% phenol should be enough to block the sympathetic supply to the lower extremity.

Complications of a lumbar sympathetic block include local anesthetic toxicity, spinal nerve root block, subarachnoid or epidural injection, renal trauma, intervertebral disc trauma, or L1 neuralgia.

Continuous Lumbar Sympathetic Ganglion Block

If consistent pain relief is seen with intermittent LSB, a continuous block should be considered. Catheters can be placed fluoroscopically using the posterior approach described above. The catheter should be placed close to the lateral portion of the anterior surface of the body of L2 on the affected side. A continuous infusion of 0.1-0.25% bupivacaine or intermittent injections of bupivacaine can be used.

Perineal Pain

Overview

The differential diagnosis of perineal pain associated with primary or metastatic tumor is extensive. Pain of neuropathic origin may occur from invasion of the lumbar spinal cord, spinal roots, sacral plexus and individual peripheral nerves. Phantom rectal pain has also been described (Boas et al, 1993; Radbruch et al, 1991).

The perineum consists of the area between the ischial tuberosities, extending from the pubis to the coccyx. The area is divided into two triangles, which are the urogenital triangle anteriorly and the anal triangle posteriorly. The somatic nerves (iliohypogastric nerve, ilioinguinal nerve, genitofemoral nerve and pudendal nerve) derives from L1, L2, and S2 to S5. The iliohypogastric nerve (L1, L2) provides sensory innervation to the suprapubic region. The ilioinguinal nerve (L1 to L2) provides sensory innervation to the skin over the inguinal ligament, base of the penis, the base of the scrotum in male or the labia in female. The genital branch of the genitofemoral nerve (L1 to L2) innervates the lateral scrotum and vulva, whereas the motor branch innervates the cremaster muscle. The pudendal nerve (S2 to S4) divides into several branches (posterior scrotal/ labial nerve, dorsal nerve, inferior rectal and perineal nerve) as the nerve exit the pudendal canal (Alcock’s canal) just medial to the ischial tuberosity. The posterior scrotal/ labial nerve innervates the posterior two-third of the scrotum/ labial majora and minor. The dorsal nerve provides sensory innervation to the penis / clitoris. The inferior rectal and perineal nerve innervates the anus and anal sphincter. Parasympathetic innervation derives from S2 to S4 and sympathetic innervation derives from T10 to L2. Due to the diverse anatomical structure and mixed sympathetic and somatic innervation, careful history taking and physical examination is required to delineate somatic verses sympathetic or visceral mediated pain. Characteristically, sympathetic or visceral pain is usually presented as vague and poorly localized pain and is frequently accompanied with burning sensation and urgency.
Sacral Subarachnoid neurolysis

Subarachnoid neurolysis of the sacral region for the management of perineal pain may be considered if limited sensory dermatomal coverage is needed (i.e. a few spinal segments). The sacral nerve roots are located at the L1-L2 level. Therefore, for sacral dermatomes, neurolysis should be performed at the L1-L2 interspace. However, it is possible to perform the block at the L5-S1 interspace where the S1 and S2 nerve roots may be spared resulting in an S3 and S4 block (Porges and Zdralhal, 1985) (Figure 5).

Intrathecal alcohol

The patient is placed in the lateral position with the affected extremity upward. The patient should be rolled forward into a 45° oblique position. This will maintain the posterior roots in the uppermost position. A spinal needle should then be placed into the intrathecal space at the L1-L2 interspace. A volume of up to 1.0 ml of 100% alcohol may be administered at a slow rate. It is recommended that a tuberculin syringe is used and increments of 0.2 ml are administered every minute. The patient may experience a transient burning sensation in the dermatomal segments to be blocked. If 1.0 ml has been reached and the painful dermatomal segments have not been blocked, then a second needle may be placed 2 spinal segments above or below the first needle placement with the same dosing procedures followed. On completion of the injection, the patient should remain in the same position for 15 to 20 minutes after which the CSF alcohol concentrations are negligible precluding any further extension of the block (Figure 6).

Bilateral blocks may be achieved with the patient in the prone position with the posterior roots uppermost. In this position, the injected alcohol will spread bilaterally to both posterior roots. Alternatively, each side can be done separately as described below.

Intrathecal phenol

The patient is placed in the lateral position with the affected extremity downward. The patient should be rolled backward into a 45° oblique position. This will maintain the posterior roots in the lowermost position. A spinal needle should then be placed into the intrathecal space at the L1-L2 interspace. A volume of up to 1.0 ml of 5 - 10% phenol may be administered at a slow rate. It is recommended that a tuberculin syringe is used and increments of 1.0 ml are administered every minute. Since phenol has local anesthetic properties, the patient should experience a feeling of warmth and tingling in the affected dermatome. If these symptoms do not occur, it has been suggested that higher concentrations should be used (Ichiyanagi et al, 1975). If 1.0 ml has been reached and the painful dermatomal segments have not been blocked, then a second needle may be placed 2 spinal segments above or below the first needle placement with the same dosing procedures followed. On completion of the injection, the patient should remain in the same position for 15 to 20 minutes after which the CSF phenol concentrations are negligible precluding any further extension of the block (Figure 7).

Because phenol is hyperbaric, it is also possible to perform a saddle block with the patient in the sitting position using 1-2 ml of 6% phenol. Although there is a risk of motor weakness and sphincteric disturbances, it is minimal and transient (Cousins, 1988).
**Sacral epidural neurolysis**

There is limited experience in sacral epidural neurolysis. There are anecdotal reports of satisfactory pain relief with lumbar and caudal epidural neurolysis with phenol; however, there is no data available. The technique is similar as described for the cervical region above (Racz et al, 1977).

**Peripheral Neurolysis**

Pudendal nerve phenol neurolysis and cryoablation may be considered for refractory pain. Transacral cryoablation of the sacral nerve roots has been described for intractable perineal pain secondary to pelvic cancer or coccydynia (Evans et al, 1981). In addition, CT guided pudendal nerve block has been described for anoperineal pain (Calvillo et al, 2000) (Figure 13A and 13B).
Ganglion Impar (ganglion of Walther) block

The ganglion Impar is a solitary retroperitoneal structure located at the level of the sacrococcygeal junction that marks the termination of the paravertebral sympathetic chains. (Cousins et al, 1998; Clemente et al, 1987). Indications for a ganglion impar block include perineal pain in patients with cancer in the cervix, colon, bladder, rectum and endometrium. Visceral phantom pain of the rectum and anus after surgical palliative intervention may also benefit from the block. (Irving et al, 1997; Warfield et al, 1993; Wesselmann et al, 1997)

Technique

The patient is placed in the lateral decubitus position. Using aseptic technique, a skin wheal is made with 1% lidocaine at the tip of coccyx. Under the guidance of fluoroscopic imaging, a 25-gauge or 22-gauge 8-cm spinal needle, which is curved manually at an angle 25 to 30˚ approximately 1.5 cm from its hub, is inserted through the skin wheal. The needle is directed anterior to the coccyx until the tip of the needle is at the sacrococcygeal junction. A smooth linear spread of contrast dye along the anterior border of the sacrum will confirm the retroperitoneal location of the needle placement. 4 to 6 ml of local anesthetic can be used for diagnostic block. Similar amount of 6 to 10% phenol or anhydrous alcohol can be used for neurolytic block once the analgesic effect of the block is established with the local anesthetic. Occasionally, excessive anterior concave curvature of the sacrum will increase difficulty of the needle placement. An alternative approach of performing the block is done with patient in prone position. Using aseptic technique and fluoroscopic guidance, a skin wheal is made with 1% lidocaine at the sacrococcygeal ligament. A 22-gauge 8-cm spinal needle is inserted through the skin wheal and the sacrococcygeal ligament. A sudden loss of resistance or a “pop” sensation will indicate the tip of the needle passing through the sacrococcygeal ligament. The needle placement is further confirmed with the injection of contrast medium. (Plancarte, et al, 1997)

Although rare, perforation of the rectum, periosteal injection, epidural injection, or sacral root injury may occur.

Vertebral Metastasis

Overview

One of the most challenging pain management problems is pain secondary to spinal metastasis. The central location of the tumor along with the complex innervation of the spine limits the use of regional anesthetic techniques for pain management. However, improvements in our understanding of the innervation of the spine has led to recent developments in which regional anesthetic techniques can be useful in managing pain.

Regional techniques for the management of pain arising from vertebral metastasis include the following: 1) vertebroplasty, 2) first and/or second thoracic nerve root block, stellate ganglion block or selective cervical nerve root block for the cervical region, 3) selective thoracic nerve root block or thoracic sympathetic block for the thoracic region, 4) first and/or second lumbar nerve root block, lumbar sympathetic block, or selective lumbar nerve root block for the lumbar region, or 5) epidural neural blockade. Vertebroplasty has been reported to be effective in the management of vertebral metastasis and is discussed in chapter (?) (Cotton et al, 1998; Gangi et al, 1994).
Anatomy

It is generally agreed upon that the spinal vertebrae and discs are highly innervated structures in which disease is capable of causing pain. However, the origin of this innervation is a point of controversy. It is generally accepted that the posterior portion of the vertebral body and discs are innervated by the sinuvertebral nerve with one sinuvertebral nerve innervating two adjacent vertebral segments (Parke, 1992). However, it is unclear as to the exact origin of spinal innervation to the anterolateral portion of the vertebral bodies and discs. It is thought that the sensory innervation of the anterolateral portion of the vertebral bodies and discs travels with the sympathetic nervous system (Bogduk, 1983). Because of this, it has also been suggested that most of the innervation to the anterolateral portion of the vertebral bodies and discs below L2 travels through the first or second lumbar nerve root and the anterolateral portion of the cervical vertebral bodies and discs travels through the first or second thoracic ganglion. If this is true, then bilateral blockade of the first or second lumbar nerve root would result in the relief of pain arising from the anterolateral vertebral bodies and discs of L2 through L5 and bilateral blockade of the first or second thoracic nerve root would result in relief of pain arising from the anterolateral vertebral bodies and discs of the cervical spine. Therefore, based on this discussion, it is important to identify the exact location of the spinal metastasis, as this will determine what regional techniques, if any, are options for the management of pain.

Cervical vertebral pain

Stellate Ganglion Block

If the pain is originating from the anterolateral portion of the cervical vertebrae, a stellate ganglion block may relieve the pain. If a consistent relief of the pain results, a continuous technique or neurolytic technique is indicated. For a discussion on these techniques, refer to section on Head and Neck.

First and/or Second Thoracic Nerve Root Block

As discussed above, the innervation of the anterolateral portion of the cervical vertebral bodies and discs is from the first or second thoracic nerve. Therefore a unilateral or bilateral first and/or second thoracic nerve root block may relieve pain secondary to metastatic disease to the cervical spine. This block is performed under fluoroscopic guidance with the patient in the prone position. In order to interrupt sensory innervation to the anterolateral portion of the cervical spine, it is necessary to block the nerve root proximal to the rami communicantes; therefore, the needle tip should be located inside the neural foramen which will often require that the needle tip be curved (Figure 13A and 13B). A volume of one milliliter of local anesthetic is sufficient to block these nerve roots.

Complications of a thoracic nerve root block include subarachnoid or epidural injection, which can result in loss of consciousness, severe hypotension or respiratory compromise. Skills of airway management are necessary for the operator of the procedure. Pneumothorax is another potentially life-threatening complication associated with the block. Block of the first thoracic nerve root may result in motor weakness of the ipsilateral upper extremity.
Selective Cervical Nerve Root Block

Pain originating from the posterior cervical vertebral body and posterior spinal segments are innervated by each segmental cervical nerve. Depending on the extent of the metastatic disease, at least one segment above and below the lesion will be required for pain control. This block is performed under fluoroscopic guidance with the patient in the supine position. In order to block both the sinuvertebral nerve innervating the posterior cervical vertebral body and the dorsal rami innervating the posterior cervical spinal segments, it is necessary to block the nerve root proximal to rami communicantes and dorsal rami; therefore, the needle tip should be located inside the neural foramen. This can be accomplished using the lateral approach; however, careful fluoroscopic guidance should be used to avoid entry of the needle tip into the subarachnoid space. An anterior oblique view fluoroscopic view will open the cervical neural foramen. From this view, the carotid artery should be palpated and identified to avoid passing the needle through the carotid sheath. Also, the needle should be advanced toward the posterior aspect of the neural foramen to avoid the vertebral artery in performing blocks and the C6 level and above. A volume of one milliliter of local anesthetic is sufficient to block these nerve roots.

Complications of a cervical nerve root block includes 1) subarachnoid or epidural injection with resulting loss of consciousness, hypotension and respiratory compromise; 2) vertebral artery injection with local anesthetic toxicity; 3) ipsilateral upper extremity weakness; 4) phrenic nerve paralysis with upper cervical nerve root blocks; 5) spinal cord injection.

Thoracic Spine

Thoracic Sympathetic Block

In the thoracic region, the sympathetic chain lies close to the neck of the ribs, and thus it is very close to the somatic roots. For pain originating from the anterolateral portion of the thoracic vertebral body and disc, a segmental thoracic sympathetic block may relieve the pain. At least one segment above and below the lesion will be required for pain relief. The procedure is performed in the prone patient under fluoroscopic guidance. The needle entry site is approximately 3 cm of the midline and advanced at approximately a 45° angle under the transverse process of the desired segment. The needle is advanced until the posterolateral aspect of the vertebral body is contacted followed by 2 ml of local anesthetic (Figure 5).

The complications of a thoracic sympathetic block include a pneumothorax and an intrathecal/epidural injection.

Selective Thoracic Nerve Root Block

Pain originating from the posterior thoracic vertebral body and posterior spinal segments are innervated by each segmental thoracic nerve. Depending on the extent of the metastatic disease, at least one segment above and below the lesion will be required for pain control. The procedure is performed in the prone patient under fluoroscopic guidance. To block both the sinuvertebral nerve innervating the posterior thoracic vertebral body and the dorsal rami innervating the posterior thoracic spinal segments, it is necessary to block the nerve root proximal to the rami communicantes and dorsal rami; therefore, the needle tip should be located inside the neural foramen which will often require that the needle tip be curved. (Figure 13A and 13B). The needle entry site is approximately 3 cm of the midline and advanced at approximately a 45° angle under the transverse process of the desired segment. The needle is then advanced into the neural foramen followed by 1 ml of local anesthetic.
The complications of a thoracic nerve root block include a pneumothorax and intrathecal/epidural injection.

**Lumbar Spine**

**Lumbar Sympathetic Ganglion Block**

If the pain is originating from the anterolateral portion of the lumbar vertebrae, a lumbar sympathetic ganglion block may relieve the pain. If a consistent relief of the pain results, a continuous technique or neurolytic technique is indicated. For a discussion on the techniques, refer to section on the lower extremity.

**First and/or Second Lumbar Nerve Root Block**

As discussed above, the innervation of the anterolateral portion of the lumbar vertebral bodies and discs is from the first or second lumbar nerve. Therefore a unilateral or bilateral first and/or second lumbar nerve root block may relieve pain secondary to metastatic disease to the lumbar spine. This block is performed under fluoroscopic guidance with the patient in the prone position. In order to interrupt sensory innervation to the anterolateral portion of the lumbar spine, it is necessary to block the nerve root proximal to the rami communicantes; therefore, the needle tip should be located inside the neural foramen which will often require that the needle tip be curved (Figure 11A and 11B). A volume of one milliliter of local anesthetic is sufficient to block these nerve roots. See paravertebral block in lower extremity section for description of the technique.

Complications of a lumbar nerve root block include subarachnoid, or epidural injection which can result in loss of consciousness, severe hypotension or respiratory compromise. Skills of airway management are necessary for the operator of the procedure. Block of the first and second lumbar nerve root may result in motor weakness of the ipsilateral lower extremity.

**Selective Lumbar Nerve Root Block**

Pain originating from the posterior lumbar vertebral body and posterior spinal segments are innervated by each segmental lumbar nerve. Depending on the extent of the metastatic disease, at least one segment above and below the lesion will be required for pain control. The procedure is performed in the prone patient under fluoroscopic guidance. To block both the sinuvertebral nerve innervating the posterior lumbar vertebral body and the dorsal rami innervating the posterior lumbar spinal segments, it is necessary to block the nerve root proximal to the rami communicantes and dorsal rami; therefore, the needle tip should be located inside the neural foramen which will often require that the needle tip be curved (Figure 11A and 11B). For a description of the technique, refer to paravertebral block in the lower extremity section.

The complications of a lumbar nerve root block include an intrathecal/epidural injection and lower extremity numbness and weakness.

**Neurolytic Techniques**

If the patient consistently achieves short-term benefit from the diagnostic blocks, then neurolytic procedures should be considered. Neurolysis can be achieved with chemical ablation (i.e. alcohol or phenol) or radiofrequency lesioning. Since motor dysfunction is not a problem
with the ablation of the thoracic nerve roots and the sympathetic chain, chemical, cryo- or radiofrequency ablation techniques can be used. However, for the cervical or lumbar nerve roots, debilitating motor dysfunction can result. For cervical and lumbar nerve root neurolysis, it is recommended that pulsed radiofrequency (RF) lesioning be used which will preserve sensory motor function. For a discussion of pulse radiofrequency lesioning, refer to neurolysis in the previous section on the role of regional anesthetic techniques for the treatment of cancer pain.

Cancer Treatment Related

Postmastectomy Pain

Prior to treating postmastectomy pain, the area of pain should be identified and therapy directed at the innervating nerve. For axillary and arm pain a second intercostal or T2 nerve root block can be performed (Figure 13A and 13B). For chest wall pain at the mastectomy site, multiple intercostal or thoracic paravertebral nerve blocks (T2-T6) may be helpful. For phantom nipple pain, a fourth intercostal nerve block can be performed (Table 3). If a prolonged response from these blocks results, repeated blocks are indicated. In addition, this block can be done in conjunction with physical therapy for patients with shoulder pain and frozen shoulder.

Reflex Sympathetic Dystrophy (RSD) has been reported to occur after mastectomy (Saddison and Vanek, 1993). If signs of RSD appear, a stellate ganglion block should be considered. If a prolonged response results, repeated blocks should be considered. RSD may result in a frozen shoulder as the patient attempts to minimize movement secondary to pain. Therefore, physical therapy in conjunction with the stellate ganglion block should be considered.

Other causes of postmastectomy pain include myofascial pain and scar pain. Myofascial pain of muscles surrounding the shoulder may be a cause of postmastectomy pain and shoulder dysfunction. Careful examination may identify trigger points in the muscles of the shoulder girdle. These trigger points may respond to local trigger point injections followed by physical therapy. Pain within the shoulder joint can result from disuse. Since over 2/3 of the intra-articular innervation of the shoulder joint is from the suprascapular nerve, blockade of this nerve performed in conjunction with physical therapy can be very valuable (Brown and Roy, 1988). In addition, a shoulder joint/bursal injection of a steroid/local anesthetic mixture may enhance rehabilitation of the shoulder. If scar pain is present, local infiltration of the scar with a steroid/local anesthetic mixture can result in long-term pain relief.

If significant physical dysfunction continues to persist, a continuous regional technique should be considered. This can be accomplished with catheters placed in the epidural space, intrapleural space or peripheral nerve. These infusions should be done together with an aggressive physical therapy program. Prolonged infusions beyond 3-4 weeks are probably not beneficial. Clear expectations should be outlined for the patient. If no improvement in physical function is seen within two weeks, the infusion should be discontinued. An epidural infusion can be accomplished with a percutaneous temporary catheter with the infusion of low concentrations of bupivacaine (1/32% - 1/8%). The tip of the catheter should be placed as close as possible to the dermatomes that supply the axilla and mastectomy site (T2-T6). Fluoroscopic guidance is useful in guiding the catheter to the side of the pain. Although less widely used, intrapleural analgesia is conceivably appropriate for postmastectomy pain. This technique has been described for mammography with needle localization and breast biopsy (Schlesinger et al, 1988). The catheter tip should be placed more toward the sulcus of the pleural cavity in order to bath the intercostal nerves that supply the axilla and mastectomy site (T2-6). Positioning should
be with the affected side up in order for the local anesthetic to layer reach the costovertebral junction and anesthetize the intercostal nerves. The use of indwelling catheters in the intercostal space has been described for the treatment of rib fractures and postcholecystectomy pain (O’Kelly and Garry, 1981; Murphy, 1983). Although the catheter is placed in one intercostal groove, the local anesthetic may reach multiple intercostal nerves by spreading vertically in the extrapleural tissue plane. Therefore, this technique can be used to treat chest wall pain as well as axillary and phantom nipple pain. A continuous suprascapular nerve infusion has been described and may be used if aggressive physical therapy is required for shoulder pain (Breen and Haigh, 1990).

If the patient consistently achieves short-term benefit from the diagnostic blocks, then neurolytic procedures should be considered. It should be kept in mind that these patients are often cured of their disease and that aggressive neurolysis is not indicated because of the risk of deafferentation pain. For postmastectomy pain, it is recommended that pulsed radiofrequency (RF) lesioning be used which will preserve sensory motor function. For a discussion of pulse radiofrequency lesioning, refer to neurolysis in the previous section on the role of regional anesthetic techniques for the treatment of cancer pain.

Cryoablation of the second intercostal nerve is also an option for the treatment of postmastectomy pain. Cryoablation is indicated for pain originating from small, well-localized lesions of peripheral nerves. Since postmastectomy pain is thought to originate from damage to the second intercostal nerve, this is a reasonable technique for pain management (Saberski, 1996). The cryolesions should be made at the inferior border of the second rib. Because the intercostal nerve runs with a large arterial and venous heat source, two 4-minute cryolesions at each level are suggested (Saberski, 1996).

Postthoracotomy Pain

The most common cause of postthoracotomy pain is surgical damage to the intercostal nerve. Therefore, if regional techniques are needed, the focus should be on the injured nerve. Initially, an intercostal or thoracic nerve root block can be performed for diagnostic purposes (Figure 5). If a prolonged response results, repeated blocks are indicated. In addition, this block can be done in conjunction with physical therapy for patients with chest wall muscle spasms.

Other causes of thoracotomy pain include myofascial pain and scar pain. Myofascial pain of the chest wall musculature may be a source of pain. Careful examination may identify trigger points in these muscles. These trigger points may respond to local trigger point injections followed by physical therapy. If scar pain is present, local infiltration of the scar with a steroid/local anesthetic mixture can result in long-term pain relief.

If significant physical dysfunction continues to persist, the continuous thoracic epidural infusion of local anesthetics should be considered. This infusion should be done together with an aggressive physical therapy program. This can be accomplished with a percutaneous temporary catheter with the infusion of low concentrations of bupivacaine (1/32% - 1/8%). The tip of the catheter should be placed as close to the injured intercostal nerve as possible. Fluoroscopic guidance is useful in guiding the catheter to the side of the pain. Prolonged infusions beyond 3-4 weeks are probably not beneficial. Clear expectations should be outlined for the patient. If no improvement in physical function is seen within two weeks, the infusion should be discontinued.

If the patient consistently achieves short-term benefit from the diagnostic blocks, then neurolytic procedures should be considered. It should be kept in mind that these patients are often cured of their disease and that aggressive neurolysis is not indicated because of the risk of
deafferentation pain. Pulsed radiofrequency (RF) lesioning and cryoneurolysis of the intercostal nerve is an option (for a discussion of pulse radiofrequency lesioning, refer above to neurolysis in the section on the role of regional anesthetic techniques for the treatment of cancer pain).

Postradical Neck Dissection Pain

Causes of postradical neck dissection pain include damage to the cervical plexus leading to neck, arm and shoulder pain and damage to the spinal accessory nerve leading to shoulder pain and dysfunction. A recent study reported complete temporary relief of neuropathic pain symptoms in 17 subjects who underwent a superficial cervical plexus block. The same study demonstrated a significant reduction in somatic pain of the shoulder area with trigger point injections (Sist et al, 1999). If a prolonged response from these procedures results, repeated blocks are indicated. In addition, these procedures can be done in conjunction with physical therapy for patients with shoulder pain and frozen shoulder. If shoulder pain and stiffness is present, blockade of the suprascapular nerve performed in conjunction with physical therapy can be very valuable (Brown and Roy, 1988). In addition, a shoulder joint/bursal injection of a steroid/local anesthetic mixture may enhance rehabilitation of the shoulder.

If significant physical dysfunction continues to persist, a continuous regional technique should be considered. This can be accomplished with catheters placed in the epidural space, or cervical plexus. These infusions should be done together with an aggressive physical therapy program. Prolonged infusions beyond 3-4 weeks are probably not beneficial. Clear expectations should be outlined for the patient. If no improvement in physical function is seen within two weeks, the infusion should be discontinued (for discussion, see Head and Neck above).

Phantom Limb and Stump Pain

The efficacy of pre-amputation regional anesthesia in reducing the incidence of phantom limb and stump pain is controversial. There are few reports in the literature on this issue. Bach et al demonstrated a reduction in the incidence of phantom limb pain in the first year after operation when using a lumbar epidural infusion of local anesthetic and opioid for 72 hours after the surgery (Bach et al, 1988). Jahangiri et al showed similar results with the perioperative delivery of epidural diamorphine, clonidine, and bupivacaine on phantom limb pain but no effect on stump pain (Jahangiri et al, 1994). In contrast, Nikolajsen et al showed no effect of perioperative epidural morphine and bupivacaine on long-term phantom limb pain or stump pain (Nikolajsen et al, 1997). In addition, Nikolajsen et al also demonstrated no long-term effects of perioperative epidural morphine and bupivacaine on stump pain (Nikolajsen et al, 1998). Using teflon catheters placed at the site of the transected sciatic nerve or posterior tibial nerve, Pinzur et al showed no long-term effect on phantom limb pain in a double blind placebo controlled study (Pinzur et al, 1996).

Patients with stump pain should be closely examined for trigger points, neuromas and myofascial pain. Local injections of these areas often result in short-term pain relief. If local treatment is insufficient in managing the pain, then the techniques described above under the upper and lower extremity can be applied for the management of phantom limb pain.
REFERENCES:


Analgesic Effects of the Cannabinoids

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INTRODUCTION
Cannabis has been utilized as an analgesic for centuries. As its therapeutic potential entered the medical literature in the mid-1800’s, its use became more widespread[1]. In the early 20th century, it became increasingly scrutinized for its psychoactive effects and recreational use and was removed from the US Pharmacopoeia in 1942[2]. However, preclinical studies continued and numerous neurobehavioral tests confirmed marijuana’s analgesic effects[3-6]. In the 1980s, more research was focused on cannabinoid receptors, and in the 1990s, the two G-protein-coupled cannabinoid receptors, CB1 and CB2, were discovered[7]. This led to a further increase in preclinical and clinical studies to assess the therapeutic potential of cannabis. Preclinical studies elucidated the sites of action of cannabinoids and showed that the brain, spinal cord, and peripheral nervous system are involved[8-11]. Many of these studies were performed using animal models that also confirmed the analgesic effects of cannabinoids in vivo.

CLINICAL STUDIES ON CANNABINOID ANALGESIA
Human studies must be interpreted carefully as there are several variables that can affect the outcomes. These include the route of administration (oral or inhaled), the drugs studied (synthetic Δ9-THC, other synthetic cannabinoids, or inhaled cannabis), and the dosages of these drugs. Other factors include the study design and whether or not it involves experimental pain or clinical pain[12].

Studies in Healthy Volunteers
Experimental studies have produced mixed results. Several studies have shown that cannabis increases the pain threshold suggesting it has an analgesic effect. [13, 14] Other studies have found either no effect on pain or even an increase in pain.[15-18] One study showed a dose-dependent effect of smoked cannabis on experimental pain.[19] Cannabis cigarettes with 2% THC produced no effect on pain, 4% THC significantly decreased pain, and 8% THC significantly increased pain. This emphasizes the above point that dosage and route of administration are likely to have a substantial effect on the results of any study.

Studies in Clinical Pain
Clinical studies that are well-designed are limited. A comprehensive literature review identified only fourteen studies that used a randomized, double-blind and placebo-controlled design. They vary in cannabinoid studied, dosages used, and routes of administration and will be discussed below grouped according to the type of pain that was studied.
**Cancer Pain**

Patients with cancer pain were the first to be studied and have also been studied the most. One study involved ten patients with various cancers and studied oral THC at 5, 10, 15, and 20 mg dosages.[20] The results showed pain relief significantly better than placebo at dosages of 15 and 20 mg, but also noted that these dosages produced substantial confusion and sedation. Another study by the same authors examined 36 patients with various cancers and compared oral THC at 10 and 20 mg dosages to codeine.[21] THC at 10 and 20 mg was found to be equianalgesic to 60 and 120 mg codeine, respectively. Again, 20 mg THC produced unpleasant drowsiness and mental cloudiness, but 10 mg THC was relatively well tolerated.

Similarly, two studies were done on patients with cancer pain looking at the effects of 4 mg of benzopyranoperidine, a synthetic analog of THC.[22] The first found it superior to placebo and equivalent to 50 mg codeine, while the second again found it superior to placebo, and also superior to secobarbital. Again, sedation was the largest side effect, but it occurred with similar instances for both the study drug and the comparison drugs. Opposite results were obtained when another group performed a similar study of benzopyranoperidine on patients with cancer pain and compared it to codeine and placebo.[23] At dosages of 2 and 4 mg, it was less effective than 60 and 120 mg codeine and was not more effective than placebo. They actually reported that pain was augmented by benzopyranoperidine and found an incidence of sedation similar to codeine. It is difficult to draw conclusions from these studies as the patient population was heterogenous (many different types of cancer pain).

**Neuropathic Pain**

Neuropathic pain is a type of chronic pain that is caused by abnormal nerve function in the peripheral or central nervous system. Common causes include diabetes, shingles, alcohol, and HIV, amongst others. Four studies have been performed on patients with various types of neuropathic pain.

The effects of oral cannabidiol were studied on ten patients with various painful neuropathies.[24] They were given a total of 450 mg/day in divided doses for one week, and no analgesic effect was demonstrated. The synthetic cannabinoid CT-3 was studied on twenty-one patients with chronic neuropathic pain and was compared to placebo.[25] Patients received 40 mg for four days and then 80 mg for three days. CT-3 use provided significant pain relief at 3 hours compared to placebo, with less of a response at 8 hours. Side effects included mild dry mouth and sedation.

A sublingual spray of either 2.7 mg THC alone or mixed with 2.5 mg cannabidiol was evaluated on forty-eight patients with neuropathic pain due to brachial plexus root avulsion.[26] Both resulted in small but significant improvements in pain as well as quality of sleep. Side effects were reported as mild to moderate and included sleepiness and dizziness. Despite small reductions of pain, most patients said it was enough that they would like to continue to use the study drugs.

The only clinical study on inhaled cannabis evaluated its effect on neuropathic pain attributed to HIV.[27] Fifty patients smoked either 3.56% THC cannabis cigarettes or placebo cigarettes three times a day for five days. Smoked cannabis significantly reduced pain by 34% compared to 17% with placebo. Side effects were mild and included sedation and anxiety.

**Acute Pain**

Acute pain is generally caused by either an injury or after surgery. It is also called nociceptive pain and is due to normal pain nerves responding to a painful stimulus of some sort. Three studies have evaluated the effects of cannabinoids on acute pain.
The first was done on people who were otherwise healthy and scheduled to receive four tooth extractions.[28] THC was administered intravenously in dosages of 0.22 and 0.44 mg/kg and compared to diazepam (valium) and placebo. Analgesia from the low dose of THC was better than placebo but less than diazepam, whereas the high dose of THC provided less analgesia than both placebo and diazepam. Anxiety and dysphoria were the biggest side effects. This effect is consistent with healthy volunteer studies that show an increase in pain with higher doses of the cannabinoids.

Another synthetic cannabinoid, levonantradol, was compared to placebo on 56 patients with acute pain.[29] Four different dosages of 1.5, 2, 2.5, and 3 mg intramuscularly all provided significant analgesia, but the authors were unable to produce a significant dose-response curve. Side effects were mild with drowsiness being the most frequent.

The effect of oral THC on postoperative pain was evaluated on forty women after having a hysterectomy.[30] On the second day after surgery, the patients were given either 5 mg oral THC or placebo. No statistically significant analgesic effect was reported, and side effects were minimal.

Chronic Pain

Chronic pain can be due to either neuropathic causes as discussed above, or nociceptive causes such as arthritis. The effects of Sativex, an oromucosal spray containing THC 2.7 mg, and cannabidiol 2.5mg, were compared to placebo on 58 patients with chronic pain due to rheumatoid arthritis.[31] Sativex produced significant pain relief with movement and at rest, improved quality of sleep, but did not decrease morning stiffness. Side effects were mostly mild to moderate with dizziness being the most common.

Another chronic pain study evaluated the effects of a sublingual spray containing either 2.5 mg THC alone, 2.5 mg cannabidiol alone, or a combination of the two, and compared them to placebo in 34 patients with chronic pain due to multiple different causes.[32] The sprays containing THC alone, and THC with cannabidiol were shown to be significantly better than placebo for relieving pain. All three sprays were significantly better than placebo for improving quality of sleep. The most frequent side effects were dry mouth, dysphoria, and sedation.

Reports on Smoked Cannabis

Several case series’ have been published discussing patients who self-medicate with cannabis. One study interviewed 15 patients who smoked cannabis for therapeutic reasons and noted that 12 of them reported improvements in pain and mood, and 11 of them reported improvement in sleep.[33] Another study performed a cross-sectional analysis of 209 chronic non-cancer pain patients and found that 15% of them reported using cannabis to treat pain.[34] They reported improvements in pain, mood, and sleep, and stated side effects were primarily dry mouth and euphoria.

A study of 30 patients who use medical marijuana at a pain center in Canada found that 93% of patients reported moderate or greater pain relief.[35] Side effects were reported by 76% of patients which included increased appetite, weight gain, and slowed thoughts. In the Netherlands, a questionnaire was sent to 300 patients who received medical marijuana for various reasons.[36] Of the 107 patients who responded, 8.6% reported they used it primarily for pain.

CONCLUSIONS

The Institute of Medicine report on the medical use of marijuana in 1999 acknowledges that cannabis can produce an analgesic effect.[37] It further recommends that additional
research be done to assess how beneficial this effect can be. As has been shown here, eight years later, only a limited amount of research has been performed. The quality of this research is quite variable and, as stated earlier, is influenced by many factors that can affect the outcomes and preclude generalizations about the effects of cannabis on pain to be made.

When one analyzes pain medicine from an evidence-based approach, it becomes apparent that there is not a lot of literature to support many practices that are commonly used daily. Pain is difficult to study because it is a subjective experience that is affected by many aspects of patients’ lives. Physicians’ clinical experience is potentially more likely than clinical studies to detect a beneficial analgesic effect from cannabis.

Preclinical studies have conclusively confirmed the analgesic effect of cannabis just as it has with many other medications. However, the clinical studies are inconclusive and suggest that there may be a therapeutic window of analgesia. Dose above this therapeutic window might increase pain. This stresses the need for further research on the analgesic effects of the cannabinoids. As long as the medicinal use of marijuana remains illegal at a federal level, the true analgesic potential of cannabis may never be known.

REFERENCES:

TABLE 1: Summary of published studies on cannabinoid analgesic efficacy.

<table>
<thead>
<tr>
<th>Study Population</th>
<th>Agent</th>
<th>Delivery Method</th>
<th>Outcome</th>
<th>Reference</th>
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<td>Healthy Volunteers</td>
<td>Marijuana</td>
<td>Smoked</td>
<td>+</td>
<td>Greenwald, 2000</td>
</tr>
<tr>
<td>Healthy Volunteers</td>
<td>Marijuana</td>
<td>Smoked</td>
<td>+</td>
<td>Milstein, 1975</td>
</tr>
<tr>
<td>Healthy Volunteers</td>
<td>Marijuana</td>
<td>Smoked</td>
<td>+ moderate doses - high doses</td>
<td>Wallace, 2007</td>
</tr>
<tr>
<td>Healthy Volunteers</td>
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<td>Oral</td>
<td>0</td>
<td>Naef, 2003</td>
</tr>
<tr>
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<td>Oral</td>
<td>0</td>
<td>Zeidenberg, 1973</td>
</tr>
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<td>-</td>
<td>Hill, 1974</td>
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<tr>
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<td>Marijuana</td>
<td>Smoked</td>
<td>-</td>
<td>Clark, 1981</td>
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<tr>
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</tr>
<tr>
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<td>Oral</td>
<td>+</td>
<td>Noyes, 1975</td>
</tr>
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<td>Oral</td>
<td>+</td>
<td>Staquet, 1978</td>
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<td>+</td>
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<td>+</td>
<td>Karst, 2003</td>
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<td>Neuropathic Pain</td>
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<td>Sublingual spray</td>
<td>+</td>
<td>Berman, 2004</td>
</tr>
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<td>Neuropathic Pain</td>
<td>THC/cannabidiol</td>
<td>Sublingual spray</td>
<td>+</td>
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<td>Neuropathic Pain</td>
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<td>Smoked</td>
<td>+</td>
<td>Abrams, 2007</td>
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<td>Intravenous</td>
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<td>Raft, 1977</td>
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<td>Acute Pain</td>
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<td>Intramuscular</td>
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<td>Jain, 1981</td>
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<td>0</td>
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<td>Sublingual spray</td>
<td>+</td>
<td>Notcutt, 2004</td>
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<td>THC/cannabidiol</td>
<td>Sublingual spray</td>
<td>+</td>
<td>Notcutt, 2004</td>
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<tr>
<td>Chronic Pain</td>
<td>Cannabidiol</td>
<td>Sublingual spray</td>
<td>0</td>
<td>Notcutt, 2004</td>
</tr>
</tbody>
</table>

+=decrease pain, 0= no effect, -=increase pain
CHRONIC SPINAL ANALGESIC DELIVERY:
A REVIEW OF THE PRECLINICAL AND
CLINICAL LITERATURE

Mark Wallace, M.D.
Professor of Clinical Anesthesiology
&
Tony L. Yaksh, Ph.D.
Professor
EARLY SPINAL DRUG DELIVERY

The demonstration by James Leonard Corning in 1885 (Corning, 1985) that cocaine delivered into the perispinal space would produce a state of hindlimb paralysis in dogs and a degree of anesthesia in man set the stage for a rapid growth at the turn of the century in which local drug delivery was used therapeutically for altering the pain state. The subsequent report by Bier in 1899 (Bier, 1899) reflecting the potent anesthetic effect in himself, his assistant and in several patients was followed by numerous reports in which local anesthetics were delivered by a number of routes including, caudal and lumbar epidural as well as cervical and thoracic intrathecal (Tait and Caglieri, 1900; Cathelin, 1901; Pagés, 1921). Although continuous intrathecal access using a catheter was achieved by Love as early as 1935 (Love 1935), a neurosurgeon at Mayo Clinic who employed this approach for CSF shunting, spinal catheters for anesthetic delivery were first described by Manalan (Manalan, 1942) and Hingson and Southworth (Hingson and Southworth, 1942). Touhey (Touhey 1945) then described the use of a catheter placed using a needle with a side-opening tip developed by Huber. Such implanted catheters with percutaneous injection ports or subcutaneous pumps permitted the long term delivery of pharmacological agents.

As reviewed in detail, MacKay (1999), the early history related to the development of spinal drug delivery evolved amazingly fast. Mackey notes that by January 1901, there had been nearly one thousand reports on this “new” anesthetic technique of spinal anesthesia. By the first decade of this century, issues related to side effects (headache; total spinal) and characteristics (anesthetic level vs concentrations, volume, baricity and the use of vasoconstrictors) were well appreciated. While much of the early work employed anesthetics, such as cocaine and concurrently synthesized analogues (such as stovaine, tropacocaine, or novocaine), the occasional effort to deliver other agents such as strychnine or morphine were reported (Marx, 1900; Matas, 1900; Matsuki, 1992) and presaged the changes in practice that arose from the rapid growth in spinal pharmacology that constitutes the focus of much of this review.

Early work emphasized the likely importance of amino acids, such as glutamate, in sensory function (Duggan and Johnston, 1970). However, the identification of the peptide substance P in small dorsal root ganglion cells (Leeman and Mroz, 1974) and the observation that opiates with a spinal action would produce a selective analgesia (Yaksh and Rudy, 1976) as well as the observation that substance P release evoked from C fibers was blocked by morphine (Yaksh, et al, 1980), marked the beginning of the current trend towards focusing on the selective regulation of spinal afferent processing (See Table 1).

Of particular importance in the evolution of spinal agents was the developing appreciation that nociceptive processes could be considered broadly divided into mechanisms that involved i) the acute activation of nociceptors; ii) the post tissue injury state in which nociceptive afferents displayed a persistent ongoing barrage and iii) change in processing that reflected changes in function after nerve injury (see Table 2)
Thus, in the middle 80’s the importance of spinal facilitatory processes to behavior was first noted by Mendell and Wall (1965, “Wind-up”). In the late 80’s, changes in spinal function secondary to peripheral nerve injury were beginning to be elucidated and preclinical models were developed that permitted assessment of the spinal pharmacology of various neuropathic conditions. In each case, preclinical behavioral models have been developed which permit assessment of the role of different transmitter-receptors systems in the several pain states. Such models confirmed the behavioral relevance in models of hyperalgesia and allodynia of excitatory amino acid receptors, of various channels (such as the N-type voltage sensitive calcium channel) and for agents believed to regulate glutamate release such as the adenosine A1 receptor. In many cases, the preclinical observations led subsequently to the implementation of the agent or family of agents in human pathological states (e.g. post operative pain states or in cancer patients). In the early work, drugs were examined in humans using acute delivery. As noted above, the technology for chronic catheter placement was however well developed and the evolution of subcutaneous ports and reliable implantable and refillable pump systems (see below) made it only a matter of time before the implementation of chronic delivery would be accomplished for the management of persistent pain states. In the following review, an overview of the analgesic action and functional characteristics of classes of agents which have been delivered in such a manner will be considered.

<table>
<thead>
<tr>
<th>Table 1. Approximate Dates of Development of Pharmacological Classes for Human Spinal Delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>μ Opiates</strong></td>
</tr>
</tbody>
</table>

*Numbers in parentheses indicate that data are from the following references: (1) 16; (2) 18,19; (3) 20; (4) 21; (5) 22; (6) 23; (7) 24,25; (8) 26; (9) 27; (10) 28; (11) 29; (12) 30; (13) 31,32; (14) 33; (15) 34; (16) 35.

Table 2. Hypothesized Components of Preclinical Pain Models

<table>
<thead>
<tr>
<th>Pain State Models</th>
<th>Stimulus</th>
<th>Time Course</th>
<th>Afferent</th>
<th>Spinal System</th>
</tr>
</thead>
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<tr>
<td>Acute</td>
<td>High-intensity</td>
<td>Acute (−s)</td>
<td>Aa/C</td>
<td>Dorsal horn nociceptive specific/Wide dynamic range/response proportional to frequency and fiber class of afferent message</td>
</tr>
<tr>
<td>Hot plate</td>
<td>thermal/mech chemical</td>
<td></td>
<td></td>
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<tr>
<td>Tail flick</td>
<td></td>
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<tr>
<td>Paw pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent/postissue injury</td>
<td>Low-intensity</td>
<td>Ongoing afferent</td>
<td>Aβ/Aa/C</td>
<td>Acute dorsal horn nociceptive specific/Wide dynamic range/response to afferent input enhanced by conditioning stimuli</td>
</tr>
<tr>
<td>Formalin (Ph 2)</td>
<td>thermal/mech</td>
<td>input (−h−d)</td>
<td></td>
<td>Induction of reorganization of biochemistry of dorsal horn receptors, channels transmitters/enzymes</td>
</tr>
<tr>
<td>Inflamed KJ/Paw Burn</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postnerve injury</td>
<td>Low-intensity</td>
<td>Ongoing afferent</td>
<td>Aa/Ao/C</td>
<td>Changes in central transport of trypic factor</td>
</tr>
<tr>
<td>Sciatic, loose lig</td>
<td>thermal/mech</td>
<td>input (−h−d)</td>
<td></td>
<td>Central sprouting of large afferents into lamina II/</td>
</tr>
<tr>
<td>Sciatic, partial lig</td>
<td></td>
<td>Sprouting, phenotype</td>
<td></td>
<td>Peripheral terminal sprout and DRG</td>
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<tr>
<td>Sciatic, freeze</td>
<td></td>
<td>changes (d-wk)</td>
<td></td>
<td>changes — persistent spontaneous activity</td>
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<tr>
<td>L5/L6 nerve lig</td>
<td></td>
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<td></td>
<td>Transynaptic degeneration</td>
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<tr>
<td>Diabetic rat</td>
<td></td>
<td></td>
<td></td>
<td>Changes in terminal transmitter/receptor synthesis</td>
</tr>
<tr>
<td>IT strychnine</td>
<td></td>
<td></td>
<td></td>
<td>Sympathetic sprouting into neuroma/DRG</td>
</tr>
</tbody>
</table>

SPINALLY DELIVERED ANALGESIC AGENTS

As reviewed above, several classes of agents have been employed for acute and chronic spinal drug delivery to ameliorate pain states. In this section, we will review their currently appreciated mechanisms of action. Preclinical investigations have led to the appreciation of spinally delivered agents with differential behavioral profiles as defined by their effects in functionally distinct pain models. Several classes of agents have been delivered spinally in humans. In the following sections, we will consider the preclinical pharmacology and mechanisms of their action (see Table 3) and then summarize the experience with their chronic spinal delivery.

Table 3. Summary of Spinal Drug Effects as a Function of Preclinical Pain Models

<table>
<thead>
<tr>
<th>Agonist</th>
<th>Opioid-μ</th>
<th>ő-</th>
<th>K</th>
<th>Opioid-E</th>
<th>K</th>
<th>Opioid-P</th>
<th>K</th>
<th>Opioid-μ</th>
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<th>K</th>
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<td>Calcium-N</td>
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</table>

Data from Yaksh et al. and Yaksh.

Opioids

Preclinical studies on spinal opiate activity

Drugs classified as opiates, interact at three principal subclasses of sites: μ, δ and K. Systematic examination of the actions these agent given spinally in the major classes of preclinical models is emphasized in Table 3. Opiates of the μ class were the first family of receptor-selective agent to be systematically examined (Yaksh and Rudy, 1976). These included meperidine, methadone, the anilinopiperadines (fentanyl, sufentanil; and alfentanil) and μ opioid peptides and β-endorphin. Subsequent work with δ (d-ala2-dleu5 enkephalin; d-penicillamine2-d-penicillamine5—enkephalin) (Schmauss, et al, 1985; Tung and Yaksh, 1985) have been shown to have a similar profile. These agents have been examined extensively in a variety of species and behavioral models. They display significant activity in models of acute nociception (e.g. hot plate and tail flick) (see Yaksh, 1987, 1997b) and are reliably potent in models of hyperalgesia induced by injury and inflammation. (Schmauss and Yaksh, 1983; Yamamoto and Yaksh, 1992a, Nagasaka, et al, 1996). K opioids (U50488, Spiradoline) given intrathecally have been shown to have typically modest effects on most acute models of nociception and slightly enhanced activity in models of inflammation and hyperalgesia (Schmauss and Yaksh, 1983; Nagasaka, et al, 1996, Pelissier, et al 1990; Malmberg and Yaksh, 1993).

μ, δ and K opiates have less predictable efficacy in models of nerve injury induced tactile allodynia (Yaksh, 1989; Yaksh, et al, 1995), but do diminish thermal hyperalgesia induced by nerve injury (Yamamoto and Yaksh, 1991).

Importantly, the μ and δ agonists at the spinal level show a reliable synergy (see below) and little if any cross tolerance (Stevens and Yaksh, 1992).
All of the above comments regarding spinal opiate action has focused on the effects of the lower doses necessary to produce antinociception. These actions appear to be functionally selective for nociceptive processing and are indeed mediated by opiate receptors. Preclinical studies have however, emphasized that at higher doses, morphine and its several congeners at higher doses can induce a variety of i) motor (e.g. clonus) and ii) sensory (pain behavior and alldynia) abnormalities. Early work clearly indicated that opiates by an opioid receptor can hyperpolarize motor horn cells (Jurna, et al, 1973). The observed motor effects appear however to mimic a possible loss of intrinsic inhibition in the motor horn (e.g. such as a loss of glycnergic tone) or a direct stimulatory effect (Curtis and Duggan, 1969). The alldynic effects are appear independent of an opiate receptor in that they are i) not naloxone reversed; ii) not stereospecific and iii) can be produced by lower doses of metabolites that have no opioid activity (e.g. morphine 3 glucuronide; normeperidine) (Yaksh, et al 1986; Yaksh and Harty 1988).

In a variety of animal models (rat, dog and primate), the chronic delivery of intrathecal μ and δ opiates by bolus or by infusion will induce a dose dependent increase in the nociceptive measure and a subsequent decline in effects over an ensuing interval ranging from 3-7 days (Yaksh and Reddy, 1981; Stevens, et al 1988; Stevens and Yaksh, 1992; Sabbe, et al, 1994). At the end of this exposure, the animal will display a right shift in the dose effect curves and a reduced maximum effect generated with bolus injections of the infused agent (Yaksh and Reddy, 1981; Stevens, et al 1988; Stevens and Yaksh, 1992; Dunbar and Yaksh, 1996). The degree of right shift produced by a given degree of drug exposure appears to correlate with the intrinsic efficacy of the opiate (Śosnowski and Yaksh, 1990; Mjanger, and Yaksh, 1991).

**Mechanisms of opiate action**

The spinal analgesic actions of the opioid agents noted above are reversed by naloxone and display a structure activity relationship which resembles that anticipated for the respective opioid receptors (see Yaksh, 1993). At the receptor levels, μ, δ (Yoshimura and North, 1983) and, on occasion, κ (Grudt and Williams, 1993) receptors can induce a membrane hyperpolarization through activation of an inwardly rectifying K+ channel. This μ receptor effect is mediated by a membrane G_{o} protein, while δ effects are mediated by G_{i/o} proteins (Carter and Medzihradsky, 1993). In addition to the hyperpolarization induced by μ and δ agonist receptor occupancy, there is a concurrent inhibition of the opening of voltage sensitive Ca^{++} channels (Kaneko, 1994; Piros, 1995), which will subsequently depress the terminal release of neurotransmitters from the cell.

Mu, delta or kappa opioid agonists with an action limited to the spinal cord will attenuate the activation of spinal wide dynamic range neurons evoked by high threshold (C fiber), but not low threshold (Aβ) afferents (Yaksh, 1978). Binding for the three opioid receptors is found in the dorsal root ganglia (Fields, et al, 1980). This observation, in conjunction with the presence of opioid binding in the substantia gelatinosa and the reduction of this binding after rhizotomy, has led to the presumption that these receptors are located on the spinal terminals of primary afferent neurons (presynaptic) as well as on cells that originate within the dorsal horn (postsynaptic). (Besse, et al 1990; Gouardères, et al., 1994). The effect of spinally administered opioids upon behavior (anti-nociception) depends upon both the presynaptic inhibition of the release of neurotransmitters from small primary afferents (such as substance P or CGRP) (Go and Yaksh, 1987; Aimone and Yaksh, 1989) and the hyperpolarization of post-synaptic neurons produced by G-protein mediated activation of potassium channels (see Yaksh, 1997b). The effects of kappa

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opioids on afferent peptide release have typically been relatively marginal (Aimone and Yaksh, 1989; Go and Yaksh, 1987). This limited effect upon small afferent transmitter release under the conditions examined may account for the modest spinal analgesic actions of these agents.

The potent effects of µ and ∂ agonists upon small sensory afferent terminal excitability provides a functional explanation for the potent effects of these agents upon behaviors driven by small afferent input (e.g. acute nociception) as well as the facilitated states that arise from persistent small afferent activation (e.g. as in the “wind-up” of dorsal horn neurons. See table 3). The effects of spinal opiates on the thermal hyperalgesia induced by nerve injury, but not the allodynia may result from the absence of opiate receptors on the spinal terminals of low threshold mechanoreceptors that are believed to mediate the evoked allodynic state (see Yaksh, 1989; Yaksh, et al, 1995).

Clinical utilization of chronic spinal opiates

Opioids are the most commonly used drugs for long-term spinal drug therapy for pain control. Morphine is the only opioid with FDA approval for long-term intrathecal delivery. When intrathecal morphine is no longer effective for pain relief, the physician may choose other opioids. Although these alternative opioids are commonly used chronically, there are very few reports on efficacy and safety. The rationale supporting the chronic use of these alternative agents is derived from the acute delivery for post-operative and labor pain.

Morphine is the “gold standard” for spinally administered drug therapy and is the only FDA approved opioid for intrathecal use. It has been demonstrated to be safe and effective for chronic delivery (see discussion under efficacy below). Table 4 summarizes the recommended conversion ratios between opioids. Although the conversion table provides a clinically useful algorithm, there are wide variations between patients. In the opioid tolerant patient, this conversion schedule is more likely to result in underdosing than overdosing.

| Table 4. Equianalgesic Opioid Conversion (mg) |
|-----------------|-------|-------|-------|-------|
| Morphi ne       | 300   | 100   | 10    | 1     |
| Hydromorphone   | 60    | 20    | 2     | 0.2   |
| Meperidine      | 3,000 | 1,000 | 100   | 10    |
| Fentanyl        | —     | 1     | 0.1   | 0.01  |
| Sufentanil      | —     | 0.1   | 0.01  | 0.001 |

There are wide variations in the total daily dose of morphine reported in the literature. For continuous delivery, the limitation to the total daily dose depends in part upon the concentration of the drug solution. The higher the concentration, the longer the pump can deliver between refills. Higher daily doses will require more frequent refills. The upper dose for morphine sulfate is limited by the apparent solubility (approximately 60 mg/mL). There are no systematic studies on the safety of such concentrations. Of further concern is that compounding drugs near the limit of their solubility raises the potential risk of precipitation within the pump and the possibility of unexpected precipitation in drug mixtures.

Other opioids that are used intrathecally include hydromorphone, fentanyl, sufentanil and meperidine. Hydromorphone is an attractive alternative choice as the kinetics are similar to morphine. It is available in concentrations up to 10 mg/ml but can be compounded to higher concentrations. There is one case report in the literature on the chronic use of intrathecal hydromorphone in combination with clonidine for the management of intractable cancer pain.
The daily dose of hydromorphone increased from 1.5 mg/day to 15 mg/day over 2 months and the addition of clonidine to the solution at 0.4 mg/day decreased the hydromorphone requirements to 5 mg/day. This dose gradually was increased to 15 mg/day of hydromorphone and 1.5 mg/day of clonidine until the patient’s death. Another case report described the use of intrathecal hydromorphone for cancer pain (Parkinson et al., 1990). Parkinson et al. used up to 2 mg/hr of intrathecal morphine which resulted in myoclonic contractions of the lower extremities. The myoclonus resolved with the discontinuation of the hydromorphone.

Two other μ opioids that deserve mention include sufentanil and meperidine. Both of these drugs are thought to have local anesthetic properties which may contribute to the analgesic effect (Hays and Palmer, 1994; Kaya et al., 1992).

The δ opioid agonist DADL (d-ala-d-leu 5 enkephalin) has been shown to be effective in long delivery in a single case study with cancer pain (Onofrio and Yaksh, 1982) and in single dose trials with cancer patients (Moulin, et al., 1985).

With regard to spinal K opioid agonists, Butorphanol, a modestly selective kappa agonist has been described to have activity in post operative pain (Abboud, et al., 1987).

Efficacy of long term spinal delivery of opiates

Morphine: Determining the efficacy of long-term intraspinal drug therapy remains one of the greatest challenges in chronic pain management. To date, there is only one published, and one unpublished controlled study evaluating efficacy of long-term intrathecal morphine. All other studies rely on retrospective reviews of large numbers of patients with a limited duration of follow-up. Therefore, the true efficacy of long-term intrathecal therapy with morphine has yet to be determined. These studies are summarized in Table 5.

One of the reasons for the lack of controlled trials is that the high cost and invasiveness of such treatment ethically precludes a double-blind, placebo controlled study design. Therefore, we can only rely on the retrospective reviews of patients receiving this therapy and attempt to make conclusions on the efficacy of this treatment. Future studies may focus on open label prospective trials with carefully designed algorithms for drug dosing or randomized controlled trials comparing intrathecal drug therapy with conventional medical management. This may allow for better conclusions on the true efficacy of long-term intraspinal drug therapy.

Many studies have attempted to determine efficacy of long-term intraspinal morphine therapy based on classification of the pain. However, review of these articles reveals large discrepancies in pain classification between studies. Because pain is often multifactorial (i.e. failed back syndrome), it is difficult to determine what pain syndromes are the most responsive to this therapy.

In a prospective study, Hassenbusch et al evaluated the efficacy of intrathecal morphine and sufentanil in 18 patients with nonmalignant neuropathic pain (Hassenbusch et al., 1990). The average follow-up was 2.4 years. Efficacy measures included pain scores, activity levels, employment status, oral opioid use, and intrathecal opioid dose. Final evaluations were conducted by an impartial third-party investigator. Overall, 61% of patients achieved an average of 39% reduction in pain scores. Seven patients were considered failures and of the remaining 11 “successful” patients, 6 used no supplemental opioids at final follow-up. Average morphine equivalent doses at the start were 13.9 mg/d and at final follow-up, 45.4 mg/d. There is one unpublished prospective study of intraspinal opioid therapy. Burchiel and Anderson screened 40 patients who had failed systemic morphine therapy (Paice et al., 1997). Their screening method...
involved a psychological evaluation and a several days to one week trial of a continuous epidural or intrathecal infusion. Thirty patients reported a greater than 50% reduction in pain with the trial and had all had pumps implanted for chronic intrathecal opioid therapy. Patients were assessed at 6, 12, 18 and 24 months for pain and function. Twenty-four month follow-up for 20 patients showed an improvement in pain and function. Mean morphine dose at 3 and 18 months were 1.96mg and 9.43 mg respectively.

Most of the retrospective studies on long-term intraspinal opioid therapy rely on a continuous epidural or intrathecal infusion using an implanted pump. There are a few studies relying on an external pump or intermittent bolusing. There are three studies in the literature using intermittent bolusing of morphine. Crawford et al reported the first series of long-term epidural morphine therapy by intermittent bolusing (Crawford et al, 1983). There series consisted of 105 patients (94 cancer and 11 non-cancer) with a mean follow-up of 65 days. The average range of daily doses of morphine was 1-6mg. 20% of the patients received either supplemental oral opioids or had local anesthetics added to the epidural regimen. They concluded that 67% of the subjects had “adequate” analgesia throughout the follow-up. Brazenor reported on a series of 19 patients who received intermittent intrathecal boluses of morphine through an implanted subcutaneous port. Seven of his cases involved the implantation of an Infusaid pump for intrathecal delivery for a total number of 26 subjects (23 cancer, 3 non-cancer) (Brazenor et al, 1987). The mean follow-up was 4.4 months and mean daily morphine doses ranged from 3-7mg for the intermittent bolusing and 1.5-21.6mg for the continuous infusion. The author concluded that 73% of the subjects received excellent pain relief during the course of therapy. Gourlay et al compared intermittent epidural and intrathecal boluses morphine with the continuous infusion of epidural or intrathecal morphine for 28 cancer patients (Gourlay et al, 1991). They looked at the effect of these techniques on pain relief, satisfaction, and estimates of neuropsychological functioning. There mean follow up was 169 days with average daily morphine doses for the epidural group being 1.8-4.6 mg. There was a 5-10 fold decrease in daily morphine requirements with the intrathecal route. They concluded that there was no difference between the two routes or techniques. These three studies support the use of intermittent bolusing either by the epidural route or intrathecal route in cancer patients with a limited life expectancy. The numbers are too small and follow-up too short to make conclusions on this technique for chronic benign pain.

There are 21 remaining reports in the literature reviewing the continuous intraspinal delivery of morphine for chronic pain. Five of these studies consist of both intrathecal and epidural delivery, 2 consist of the epidural route only and the remaining are intrathecal delivery only. Three of the studies used external pumps to delivery morphine through a port or externalized catheter and are summarized as follows. Arner et al presented the results of a large nationwide survey on the epidural and intrathecal delivery of morphine for cancer pain (741 cases) and non cancer pain (19 cases) (Arner et al, 1988). Mean follow-up was 4 months and the daily peak morphine doses were 46mg for the epidural group and 9.6mg for the intrathecal group. Although the article supported the safety of this technique, no conclusions could be made on outcome. Plummer et al reported a series of 313 patients who received either epidural (295) or intrathecal (18) morphine delivered through a catheter with a subcutaneous access port (Plummer et al, 1991). The mean follow-up was 155 days and the daily dose range for the epidural delivery was 22-107mg and the intrathecal delivery 1.6-21mg. Conclusions on efficacy were not presented, however, they stated only two catheters were explanted due to inadequate pain relief. Yue et al reported on a series of 53 patients who received continuous epidural morphine or hydromorphone through an externalized catheter for pain control (Yue et al, 1991). The mean follow-up was 76.3 days and the mean daily morphine dose was 13.7 mg. They stated
that prior to treatment, the patients' pain scores ranged from 7-10 out of 10. Mean post treatment pain scores were 1.9 out of 10. Eight patients with RSD required addition of local anesthetic for pain relief.

There is one study in the literature using an implanted pump for the epidural delivery of morphine. Hassenbusch et al used an implanted pump to deliver a continuous epidural infusion of morphine in 41 cancer patients. Mean follow-up was 7.1 months and the dosing range was 20.7 – 49.3 mg/day. They reported that 81.2% of the subjects had at least a 30% reduction in pain at 6 months.

There are four studies using an implanted pump for continuous epidural or intrathecal delivery of morphine. Coombs et al reported a series of 5 cancer and 5 non-cancer patients who received epidural or intrathecal morphine through an implanted pump (Coombs et al, 1983). Mean follow-up was 3 months and the mean daily morphine requirement was 3.2-8mg. Differences between the epidural and intrathecal dose could not be determined from the article. They concluded that the cancer patients had a 50% reduction in pain and the non-cancer patients had no change in pain. A weakness of this study is the short follow-up and low peak mean dose even for intrathecal delivery. The failure in the non-cancer group may be the result of underdosing with the morphine. A follow-up to this report involved 14 cancer patients with an implanted pump delivering morphine epidurally or intrathecally (Coombs et al, 1984). The mean follow up was 5.6 months and daily doses of morphine ranged from 2-50mg for the epidural group and 0.5-75 mg for the intrathecal group. The authors concluded that at 6 months, there was marginal pain control despite massive oral and/or parenteral opioids. The only difference between these two studies is the follow-up period. The failure in Coombs et al second study may be due to progression of disease over the additional 2-3 months. Krames et al reported a series of 16 cancer and 1 non-cancer patient who received epidural or intrathecal morphine through an implanted pump (Krames et al, 1985). Mean follow-up was 5.6 months and mean daily morphine doses were 4.6-9mg for the epidural group and 1.75-7.6mg for the intrathecal group. Their patients reported a 50-70% reduction in pain scores but all patients required oral analgesics. These four studies support the use of intraspinal opioids for the treatment of cancer pain, however, outcome conclusions cannot be made because they are poorly controlled and they lack information on costs. Ultimate failures in this group are most likely the result of disease progression.

As the intrathecal route of delivery became more popular in the late 1980s and 1990s, there have since been many reports on the use of an implanted device for continuous intrathecal morphine delivery in nonmalignant pain. Auld et al reported a series of 43 patients who received intrathecal morphine for nonmalignant pain (Auld et al, 1985). Mean follow-up was >24 months and no one exceeded 7mg/day of intrathecal morphine. They concluded that 65% of the patients had good to excellent pain relief. Of 15 potentially employable patients, eight returned to some form of work. All of the patients who failed therapy had “failed back syndrome”. In a series of three patients with reflex sympathetic dystrophy, Goodman and Brisman used intrathecal morphine via an infusaid pump. Mean follow –up was 12 months. Two out of the 3 patients reported a 50-70% reduction in pain. They did not report the daily morphine dose. Onofrio et al reported on 53 cancer patients who received continuous intrathecal morphine (Onofrio et al, 1990). Mean follow-up was 4 months and the average range of daily morphine was 3.8-9.5 mg. They concluded that 67% were defined as having good to excellent pain relief during follow-up. Follett et al reported on 37 patients who received continuous intrathecal morphine (Follett et al, 1992). Mean follow-up was 7.7 months with an average daily morphine dose of 5.4 mg. Efforts were made at maintaining a pain level of less than 2-3 out of 10 which was successfully achieved in 77% of the patients. Krames et al gave the first report on the use of the Synchromed Infusion
System for chronic intrathecal morphine or hydromorphone delivery in 16 patients with nonmalignant pain (Krames et al, 1993). Mean follow-up was 27.8 months and the average daily morphine dose was 1.7-8.9 mg. Bupivacaine was added to the morphine solution in 13 of the 16 patients. Overall, 81% reported good to excellent relief. Strengths of this report are the relatively long follow-up compared to other studies. A weakness is the small sample size. A similar study was published by Kanoff. They studied 15 patients with nonmalignant pain with an average follow-up of 17 months and peak daily morphine requirements of 19 mg (Kanoff et al, 1993). They reported a 73% good to excellent relief of pain. Chambers et al reported on 15 patients with malignant (12) and nonmalignant (2) pain who received chronic intrathecal morphine (Chambers et al, 1994). Mean follow-up was 14 weeks and the peak average daily morphine requirement was 9.4 mg. They reported a 99% good to excellent pain relief. Becker et al reported on 2 patients with nonmalignant pain who received chronic intrathecal morphine (Becker et al, 1995). Mean follow-up was 59 months and the daily morphine dose was not given. They concluded a “relatively satisfactory” pain relief but their report is limited by the small number of patients. Tutak et al reported on 26 patients with nonmalignant pain who received chronic intrathecal morphine (Tutak, 1996). Mean follow-up was 23 months and average daily dose of morphine was 1.4-9.3 mg. The average preimplantation pain score was 8.9 out of 10 and the average pain score at 12 months was 4.9 out of 10. Overall 77% of the subjects noted a good to excellent outcome. There was a 59% average subjective pain relief and a 50% average increase in daily function. Yoshida et al reported on a series of 18 patients with failed back who received continuous intraspinal morphine. The mean follow-up was 24 months and they concluded that this technique should not be used for chronic nonmalignant pain as they had only a 25% success rate. However, daily doses were not mentioned in the study making it difficult to make conclusions on efficacy. Paice et al published a survey of 35 physicians who had implanted more than 5 Synchromed infusion systems. This survey provided 429 patients for evaluation with a mean follow-up of 14 months. The mean daily morphine dose ranged from 6.8 – 13.1 mg. They concluded that there was a mean 61% pain relief. The most comprehensive study to date on the efficacy of chronic intrathecal opioids is published by Winkelmuller et al. They reported on 120 patients who received chronic morphine for pain of nonmalignant origin. The mean follow-up was 41 months and the average daily morphine requirements were 2.7-4.7 mg. They concluded that there was a 58% mean pain reduction as of the last follow-up. Ninety-two percent of the patients were satisfied with the therapy and 81% reported an improvement in their quality of life. Strengths of this report are the large number of subjects studied and the long follow-up. A weakness is the subjectiveness of the quality of life measurement as this was assessed with a single question to the patient and not a more detailed questionnaire.
Morphine/Bupivacaine Combination: Even with high dose intraspinal opioids, some pain syndromes do not respond and a logical next step is the addition of local anesthetics. There are several reports in the literature using this method with most of them reviewing cancer pain. However, like the studies on intraspinal morphine alone, studies on opioid/local anesthetic mixtures are very limited and no strong conclusions can be made. Table 6 summarizes these studies.

Berde et al were one of the first to report on the use of continuous intrathecal bupivacaine for refractory pain in a spinal cord tumor patient (Berde et al, 1990). They used daily doses ranging from 240 to >800 mg. They reported satisfactory pain relief but the patient developed tachyphylaxis on several occasions requiring drug holidays. Du Pen et al also published a case report on 2 cancer patients who received an epidural morphine/bupivacaine infusion. Mean follow-up was 2 months and the mean daily bupivacaine dose was 225 mg. Both patients achieved good pain control (Du Pen et al, 1992).
Nitescu et al reported on a series of patients who had a bupivacaine/morphine mixture for the control of cancer pain (Nitescu et al, 1990). Their series consisted of both epidural and intrathecal infusions and mean follow-up was 50 days. The mean daily dose of bupivicaine was 60-75 mg epidurally and 15-20 mg intrathecally. They concluded that there was more satisfactory pain relief from the intrathecal delivery than with epidural delivery.

Hassenbusch et al reported on a case series of 4 patients with nonmalignant pain who received an epidural bupivacaine/morphine combination (Hassenbusch et al, 1991). Mean follow-up was 12 months and the mean daily bupivacaine dose ranged from 1-14.4 mg. They concluded that there were no significant differences noted between the morphine vs morphine/bupivacaine infusions. They used very dilute solutions of bupivacaine which most likely resulted in an underdosing of the patients. Another report on the use of a morphine/bupivacaine intrathecal infusion for nonmalignant pain was published by Krames et al (Krames et al, 1993). They reported on the use of this method in 13 patients using a Synchromed infusion system. Mean follow-up was 11.3 months and mean daily bupivacaine dose range was 3.7-4.1 mg. They concluded that the addition of bupivacaine either decreased opioid side effects or increased analgesia in 77% of patients.

Sjoberg et al has the largest series of patients in two reports published in 1991 and 1994 (Sjoberg et al, 1991; Sjoberg et al, 1994). Their 1991 reports consisted of 52 cancer patients who received an intrathecal infusion of a morphine/bupivicaine combination. Mean follow-up was 23 days and total daily bupivacaine dose was 60-70 mg. They published a second report in 1994 on 53 cancer patients who received the same therapy. Mean follow-up was 29 days and mean daily bupivacaine dose range was 3.8 – 47.5 mg. Both reports concluded that all patients achieved adequate pain control until death.

Finally, Van Dongen reported on 17 cancer patients who received an intrathecal morphine/bupivacaine infusion (Van Dongen et al, 1993). Mean follow-up was 112 days and mean daily bupivacaine doses ranged from 10-100mg. They concluded that 10 (58%) of the patient who failed opioid therapy alone achieved adequate analgesia with the addition of bupivacaine.

These studies demonstrate that patients with pain refractory to intraspinal opioids alone may respond to the addition of a local anesthetic. These studies report a wide range of daily bupivacaine doses with few side effects. However, it is difficult to make conclusions on recommended daily doses as end-stage cancer patients are likely to tolerated much higher doses since they are more likely to be bedridden. The only study using bupivacaine for nonmalignant pain is from Krames et al and they only used up to a mean of 4.1mg/day without any side effects. As with opioids alone, further studies are warranted in this area.
Side effects

There are many drug related side effects with intraspinal delivery. Rarely are these side effects serious or life-threatening and are usually reversible on decreasing the dose or discontinuing the drug. Winkelmuller et al presented the most extensive review of the side effects with long-term intraspinal morphine (Winkelmuller et al, 1996) (Table 7). They stated that most of these side effects spontaneously resolved with the exception of sweating and peripheral edema which persisted. Other less common side effects that have been reported in the literature include paranoia (Christie et al, 1993), hyperalgesia/myoclonus (Ali, 1986; De Conno et al, 1991; Parkinson et al, 1990); meniere-like symptoms (Linder et al, 1989); nystagmus (Fish et al, 1990; Ueyama et al, 1992) and polyarthralgia (Krames and Lanning, 1993).

Whereas most side effects of intrathecal morphine are not always dose-related, bupivacaine induced side effects are dose related. These side effects are related to the anesthetic effects of the bupivacaine at the spinal level and include parasthesias, motor and sensory blockade, arterial hypotension and urinary retention (Sjoberg et al, 1991). Diarrhea has also been reported with the use of intrathecal bupivacaine (Krames and Lanning, 1993). All of these side effects begin occurring at daily doses of >45mg/day (Sjoberg et al, 1991; Sjoberg et al, 1994). However, these dosing recommendations were acquired from cancer patients with a limited follow-up. End stage cancer patients are often bedridden making it difficult to make conclusions on efficacy and side effects.

<table>
<thead>
<tr>
<th>Study</th>
<th>Cancer Patient No.</th>
<th>Normal ig Patient No.</th>
<th>Mean Follow-up</th>
<th>Average Range of Bupivacaine mg/24 h</th>
<th>Method of Delivery</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td>Berde, 1990</td>
<td>1</td>
<td>0</td>
<td>7 mo</td>
<td>240 — 800</td>
<td>IT, continuous</td>
<td>Tachyphyaxis occurred on several occasions. Infusion used until death</td>
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<td>Bupivacaine</td>
<td></td>
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<td></td>
<td></td>
<td>More satisfactory pain relief with intrathecal delivery</td>
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<tr>
<td>Milecki, 1990</td>
<td>20</td>
<td>0</td>
<td>50 d — EPI</td>
<td>60—75 mg EPI</td>
<td>EPI, continuous</td>
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<tr>
<td>Bupivacaine +</td>
<td></td>
<td></td>
<td></td>
<td>37 d — IT</td>
<td>IT, continuous</td>
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<td>15—20 mg IT</td>
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<td>0</td>
<td>4</td>
<td>12 mo</td>
<td>1—14.4</td>
<td>Synchronized Epidural</td>
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<td>Sjoberg, 1991</td>
<td>52</td>
<td>0</td>
<td>23 d</td>
<td>60—70 mg/d</td>
<td>IT, continuous</td>
<td>Good to excellent relief in 86% of patients</td>
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<td>Morphine</td>
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<td>Cakmak, 1992</td>
<td>2</td>
<td>0</td>
<td>2 mo</td>
<td>225 mg/d</td>
<td>EPI, continuous</td>
<td>Good pain control until death</td>
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<tr>
<td>Krames, 1993</td>
<td>0</td>
<td>13</td>
<td>11.3 mo</td>
<td>3.7—4.1 mg</td>
<td>Synchronized IT, continuous</td>
<td>The addition of bupivacaine either decreased opioid side effects or increased analgesia in 77%</td>
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<td>Van Dongen, 1995</td>
<td>17</td>
<td>0</td>
<td>112 d</td>
<td>10—100 mg</td>
<td>IT, continuous</td>
<td>17 patients who failed opioid therapy alone had bupivacaine added. 10 (53%) achieved adequate analgesia.</td>
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<td>Sjoberg, 1994</td>
<td>53</td>
<td>0</td>
<td>29 d</td>
<td>3.8—47.5 mg</td>
<td>IT, continuous</td>
<td>Significant reduction in opioid consumption Acceptable pain relief in 100% of subjects</td>
</tr>
</tbody>
</table>

Data from references 130–116.
Alpha-2 adrenergic agonists

Preclinical studies on spinal activity

The spinal delivery of adrenergic agonists were early demonstrated to produce a potent antinociception on models of acute nociceptive processing (Reddy and Yaksh, 1979; Reddy, et al, 1979) as well as on models of facilitated processing (see Table 3). Initial work emphasized that the adrenergic agonists exerted their effects by an alpha 2 subclass of receptor. As with opiates, they are active in models of thermal hyperalgesia, but unlike opiates, they display considerable potency in models of nerve injury evoked tactile allodynia (Yaksh, et al, 1995).

It is currently appreciated that there are several subclasses of alpha 2 receptors as defined by messenger RNA and binding (McKinnon, et al 1994; Bylund, 1995). Although studies in knock out mice suggest a role for the alpha 2a (Lakhlani, et al, 1997), other receptors may also be relevant. Pharmacological studies have suggested that the antinociceptive action at the spinal level may be mediated by multiple classes (Takano and Yaksh, 1992).

Animal studies have demonstrated that continuous delivery or repeated administration of spinal alpha 2 agonists will result in a right shift in the dose effect curve and a reduced maximum (Yaksh and Reddy, 1981; Stevens, et al 1988; Yaksh, et al, 1994). Takano and Yaksh (1992) assessed the development of tolerance in rats exposed to chronic IT infusions of clonidine, ST-91 and dexmedetomidine. All three drugs exhibited tolerance development over a seven day period. There was cross tolerance between clonidine and both dexmedetomidine and ST91, but no cross tolerance between dexmedetomidine and ST91. This suggests that there may be two alpha-2 adrenergic receptor subtypes, both of which are affected by clonidine. Of the three drugs, dexmedetomidine showed the least rightward shift in dose response curve following seven day exposure, suggesting a greater intrinsic activity, or receptor reserve.

Mechanisms of action

The system underlying the spinal action of alpha2 agonists is comparable to that employed by spinal opiates: i) Alpha 2 receptor binding is presynaptic on primary afferents and post-synaptic on dorsal horn neurons (Howe, et al, 1987; Bouchenafa and Livingston, 1987). ii) While it is not clear that this binding is on C fibers (Wikberg and Hajos, 1987), alpha2 agonists clearly depress release of C fiber transmitters such as substance P and CGRP (Ono, et al, 1991; Takano, et al, 1993; Bourgoin, et al, 1993); and, iii) Alpha 2 agonists hyperpolarize dorsal horn neurons through a Gi coupled K channel (North, et al, 1987). The above characteristics do not uniformly explain why spinal alpha 2 agonists are effective against tactile allodynia in contrast to spinal opiates (see Table 3). It has been hypothesized that the spinal alpha 2 receptor
suppresses preganglionic sympathetic outflow and may accordingly be effective in pain models that are dependent upon sympathetic drive (Yaksh, et al, 1995).

Clinical utilization of chronic spinal alpha 2 adrenergic agonists

Clonidine (Duraclon) is currently FDA approved for epidural use in cancer pain only. However, there are reports of the use of intrathecal clonidine for both cancer and nonmalignant pain (see below under efficacy). Daily intrathecal doses as high as 400 µg have been reported with no untoward effects (Borg, 1996). Tramadol produces analgesia through both opiate and adrenergic mechanisms. Epidural administration of doses high enough to provide significant systemic analgesic effect (50 to 100 mg) were shown to produce postoperative analgesia in humans (Delikan and Vijayan, 1993; Baraka et al., 1993), but it is not clear from these clinical studies whether the epidural route is associated with a significant spinal mechanism of action.

Clonidine is an alpha-2-agonist with demonstrated analgesic efficacy in preclinical studies. However, human studies are far and few and this agent was recently approved for epidural administration for the management of cancer pain only. There are several reports in the literature on the use of this agent for the management of nonmalignant pain delivered by both the epidural and intrathecal route. Table 8 summarizes these studies.

The first report of the use of intrathecal clonidine for chronic pain was published by Coombs et al who used intrathecal clonidine for the management of intractable cancer pain (Coombs et al, 1986). The patient was resistant to intrathecal hydromorphone and the addition of clonidine at 400 µg/day successfully treated the pain. Daily dose at death was 1500 µg/day.

The first human study was reported by Eisenach et al who treated 7 cancer patients with a continuous morphine/clonidine combination delivered epidurally. There follow-up was up to 5 months in one patient and the daily clonidine dose ranged from 240 – 1680 µg/day. They reported good analgesia with fewer side effects with the addition of clonidine (Eisenach et al, 1989).

Since this initial study, there have been several case reports on the use on intraspinal clonidine in combination with other agents. Siddall et al published a case report on a spinal cord injury patient refractory to intrathecal morphine for pain management (Siddall et al, 1994). The addition of clonidine at 8 µg/day resulted in a significant reduction in pain. At 9 months follow-up, the patient still reported good pain relief with morphine/clonidine at 5mg and 17µg per day respectively. Borg et al also reported a case report series of four patients who received a combination of intrathecal clonidine and midazolam for chronic benign pain (Borg et al, 1996). Mean follow-up was 2.5 years and the average daily dose was 390 µg. They reported good pain control in all subjects. It was unclear as to why they chose this combination of drugs. Finally, Middleton et al reported on a patient with spinal cord spasticity who was refractory to intrathecal baclofen up to 450 µg/day (Middleton et al, 1996). The addition of clonidine at 50 µg/day resulted in a significant reduction in spasticity.

The most convincing studies on the efficacy of intraspinal clonidine are from Rauck in 1993 and Eisenach in 1995. Rauck et al reported on a series of 19 patients with reflex sympathetic dystrophy who received a continuous epidural infusion of clonidine (Rauck et al, 1993). All patients were screened with a single epidural injection of clonidine in a placebo-controlled blinded fashion and those who responded were given the option of a continuous infusion. Mean follow-up was 43 days with an average daily clonidine dose of 768 µg. Mean pain scores decreased from 7.1 out of 10 preinfusion to 5.1 out of 10 postinfusion. Side effects were mild and transient and did not result in any patient discontinuing therapy.
The largest study to date was published by Eisenach et al who used a double-blind placebo controlled trial of epidural clonidine for the management of cancer pain (Eisenach et al, 1995). They used epidural morphine as a rescue. Mean follow-up was 8 weeks and the total daily dose used was 720 µg. They reported that pain relief was better in the clonidine group but there was no difference in morphine requirements between groups. They also noted that clonidine was quite effective in the management of neuropathic pain.

**Side Effects**

There are few side effects associated with clonidine even at higher doses. The most common side effects are hypotension, bradycardia, and sedation (Eisenach et al, 1995; Rauck et al, 1993). These side effects are often well tolerated and do not necessitate discontinuation of the drug. The hypotensive effect of intrathecal clonidine likely occurs secondary to the effects of the drug on the preganglionic fibers in the thoracic spinal cord (Eisenach and Tong, 1991). The sedative effect most likely occurs secondary to actions primarily in the locus coeruleus in the brainstem (Correa-Sales et al, 1992).

**N-type voltage sensitive Calcium Channel Blockers.**

**Preclinical studies on spinal activity**

Intrathecally delivered N-type Ca Channel antagonists are effective in several preclinical models of facilitated processing, such as those which involve tissue injury or inflammation (Malmberg and Yaksh, 1994) or nerve injury or diabetes (Chaplan, et al; 1994; Bowersox, et al, 1996; Calcott and Chaplan, 1997) giving rise to hyperalgesia and allodynia. At doses which do not alter motor function, acute bolus delivery has little effect upon acute thermal nociception (Malmberg and Yaksh, 1994; Chaplan, et al; 1994).

Continuous spinal delivery in rat models displays little change in the antihyperalgesic action over a brief 7 day exposure. Interestingly, with continuous exposure, acute thermal escape latencies were elevated (e.g. appeared to be a modest regulation of acute thermal nociception (Malmberg and Yaksh, 1995).

**Mechanisms of action**

Localization studies with SNX-111 binding or subunit antibodies indicate that N-type channels are in high levels in the substantia gelatinosa (Gohil, et al, 1994; Westenbroek, et al, 1998) and are frequently found on membranes of profiles that contain substance P. Extensive characterization of the role of N-type calcium channels in dorsal root ganglion cells emphasize their role in transmitter release (Diverse-Pierluissi and Dunlap, 1995). Blockade of N-type channels will reduce dorsal horn glutamate release (Gruner and Silva, 1994). This effect upon glutamatergic transmission and the role of spinal glutamate in facilitatory states is thus
consistent with the observed profile of intrathecal N-type voltage sensitive calcium channel blockers.

Clinical utilization of chronic spinal N-type calcium channel blockers

Recent studies have shown that an intrathecal N-type Ca channel antagonist (Ziconotide) will attenuate neuropathic pain conditions in patients suffering from neuropathic and cancer pain (Presley, 1998). Daily doses range from 2.5-25 µg. It is currently being evaluated in a multicenter study as an intrathecal agent for the treatment of chronic malignant and non-malignant pain. Preliminary results from the multicenter double-blind placebo controlled study were reported by Presley et al (Presley et al, 1998). The study included 259 patients with chronic opioid resistant pain secondary to a wide variety of neuropathic pain syndromes. There was a significant decrease in pain with the use Ziconotide. Common adverse events were dizziness, nausea, nystagmus, gait imbalance, confusion, constipation and urinary retention. These adverse events resolved with dose decrease or discontinuation. A long-term open label trial is currently underway. Ziconotide has also been demonstrated effective for acute nociceptive pain (Atanassoff et al, 1998).

Side Effects

Common side effects with Ziconotide include dizziness, nausea, nystagmus, gait imbalance, confusion, constipation and urinary retention (Presley et al, 1998). These side effects usually occur after prolonged use of the drug and are dose related. They usually resolve with a decrease in dose or drug discontinuation.

Somatostatin

Preclinical studies on spinal activity

SST1-28 (Somatostatin-1-28) is an endogenous peptide which given intrathecally has been reported to exert modest analgesic effects in acute nociceptive and hyperalgesic states (Ono, et al, 1997, but see Traub and Brozoski, 1996). In many preclinical studies, doses necessary to block the pain behavior are little different from those at which motor dysfunction is observed (see Gaumann and Yaksh, 1988; Long, 1988; Mollenholdt, 1990) The subject has been a point of considerable controversy (see Yaksh, 1994).

Mechanisms of action

The effects of intrathecal somatostatin are likely mediated by one or more of the five somatostatin receptors have been cloned and are referred to as SSTR1-SSTR5.(Rescine, and Bell, 1995). Several of these receptors are found in the primary afferents and in the spinal gray matter, while other show significant concentration in the ventral horn (Senaris, et al, 1995; Schindler, et al 1997, 1998). Electrophysiologically, somatostatin 1-28 can hyperpolarize a cell though a G protein coupled inwardly rectifying K current (Shen and Surprenant, 1993) and block opening of coupled calcium channels that serves to reduce transmitter release (Dichter, et al, 1990). Conversely, it should be emphasized that somatostatin 1-28 can produce significant depolarization. (Delfs and Dichter, 1983) in part by augmenting the synaptic actions. This could occur by : i) an action at glutamate synapses (Wang, et al, 1993); increasing increase in PLA-2 activity to release arachidonic acid (Schweitzer, et al, 1993). In addition, SST1-28 is cleaved by a variety of endopeptidases (Lucius and Mentlein, 1991) and the activity of these cleavage products are likely biologically relevant with activity profiles that are distinct from the parent. The role of the several fragments have not been systematically investigated. Moreover,
the multiple somatostatin receptors are clearly functionally distinct. While most of these are believed to be negatively coupled to the synthesis of cyclic AMP, splice variants exist that may not (Resin, et al, 1993; Patel, et al, 1994).

Clinical utilization of chronic spinal somatostatin agonists

The literature on the spinal analgesic actions of SST_{1-28} or an analogue (SST_{1-8}) in humans is largely anecdotal and controversial. Somatostatin was reported to have analgesic actions in post operative and cancer pain (Chrubasik, et al 1984; 1985; Meynadier, et al, 1985) states, though such efficacy was considered controversial when examined in blinded studies (Desborough, et al, 1989). Intrathecal Octrotide was reported effective in two non malignant pain patients (Paice, et al, 1996). In 6 of 8 patients suffering in the terminal stages of malignancy, somatostatin 1_{-28} was able to produce some degree of pain relief. All patients showed a very rapid escalation of drug dose over the brief period infusion, perhaps reflecting either the rapidly excavating pain state or a very rapid tolerance (Mollenholdt, et al, 1994).

There is little doubt that SST can influence spinal nociceptive processing. It is reasonable however to hypothesize, given the multiple receptors populations that exit in the spinal cord, that its controversial effects and potential toxicity may be associated with one or more of the 5 subtype receptors. The development appropriate analogues for these several classes of receptors may provide insight and appropriate prospects for development (see for example Rainier, et al, 1993).

NMDA (N-methyl-d-aspartate) receptor antagonists

Preclinical studies on spinal activity

Preclinical studies have shown that intrathecal NMDA antagonists have little effect upon acute nociception, but are able to diminish hyperalgesia and allodynia in models of tissue injury (Yamamoto and Yaksh, 1992a; Ren and Dubner, 1993 Chapman, et al, 1997); and nerve injury (Yamamoto and Yaksh, 1992b; Mao, et al, 1993; Sherman and Loomis, 1996).

Mechanisms of action

The NMDA receptor, a calcium ionophore, is activated by glutamate. This receptor has been isolated, cloned and consists of two principle gene products (R1 and R2) which must be co expressed to form a functional receptor. For the NMDA-r 1 8 splice variants have been identified along with 4 distinct isoforms for NMDA-R2 (Sucher, et al, 1996). These several isoforms are functionally distinct and likely account for the differential distribution of binding observed with different ligands, as well as varying sensitivities to different cofactors and channel modulators. The release of glutamate and occupancy of the NMDA-r serves to depolarize the membrane and increase intracellular calcium. The opening of the channel is regulated by several additional components: i) a magnesium block that is removed by membrane depolarization; ii) allosterically coupled sites occupied by glycine and polyamines required for channel activation and iii) phosphorylation sites that serve to enhance glutamate-evoked NMDA-r opening. The opening of the channel may be prevented by i) competitively antagonizing the occupancy by glutamate of the receptor; ii) blocking the channel or iii) by blocking the allosterically coupled glycine site (Lodge and Johnson, 1990).

NMDA binding is elevated in the substantia gelatinosa and dorsal horn (Mitchell and; Anderson, 1991; Shaw, et al, 1991) and in dorsal root ganglia (Sato, et al,1993). Tissue injury evokes a significant increase in spinal glutamate release (Malmberg and Yaksh, 1995; Yang, et al, 1996) and this results in a well defined allodynia and hyperalgesia, mediated by the activation of
the NMDA receptor. These results are in accord with the ability of spinally delivered NMDA antagonists to block central facilitation initiated by persistent small afferent input (e.g. wind up: Chapman and Dickinson, 1992).

**Clinical utilization of spinal NMDA antagonists**

Ketamine, a non competitive NMDA antagonist has been given epidurally for postoperative pain with modest results (Islas et al., 1985; Ravat et al., 1987; Naguib et al., 1986). There is little information regarding the use of intrathecal NMDA antagonists in chronic pain states. Spinal administration of CPP a competitive NMDA antagonist suppresses allodynia but not spontaneous pain in a patient with a peripheral nerve injury (Kristensen et al., 1992). Most of the report on the efficacy of long-term intraspinal ketamine are anecdotal. There are several reports on use of ketamine/morphine combinations for terminal cancer pain with good results (Yang et al, 1996; Muller and Lemos, 1996). There are also questions about the toxicity of chronic intraspinal ketamine. Karpinski et al reported on a case of a terminal cancer patient who received a 3 week intrathecal infusion of ketamine prior to death. An autopsy demonstrated subpial vacuolar myelopathy (Karpinski et al, 1997). The long-term safety of intrathecal ketamine is unclear.

**Adenosine**

**Preclinical studies on spinal activity**

Adenosine exerts an action at least two receptors. Adenosine A1 agonists given intrathecally will induce a modest effects in elevating acute nociceptive thresholds (Sawynok et al., 1986; Sosnowski, et al, 1989a), but serves to markedly diminish the hyperalgesia and allodynia induced by tissue injury and peripheral nerve injury (Sosnowski and Yaksh, 1989b; Lee and Yaksh, 1996; Sjolund, et al 1999). Endogenous adenosine has a tonic inhibitory effect, and that it is may be involved in the analgesic effect of large afferent fiber stimulation (Salter and Henry, 1987). This might account for the efficacy in neuropathic conditions.

**Mechanisms of action**

A1 receptors are located in high concentrations in the substantia gelatinosa, but they appear to be largely on non primary afferent terminals (Geiger and Nagy, 1985; Choca, et al 1988), a finding consistent with the inability of A1 agonists to block substance P release from primary afferents (Vasko and Ono, 1990). Current evidence suggests adenosine, through the A1 receptor, may diminish glutamate release from spinal systems (Conway and Yaksh, 1998; Kakinohana, et al , 1998). Consistent with this effect upon spinal glutamate release, single unit recording form dorsal horn wide dynamic range neurons emphasize that A1 agonists can diminish wind up without altering Aß evoked activity. (Reeves and Dickenson, 1995).

**Clinical utilization of spinal adenosine agonists**

In humans, consistent with the preclinical observations, acute delivery of the adenosine A1 selective agonist has been shown to diminish the allodynia elicited by vibration and touch in neuropathic pain patients (Karlsten and Gordo, 1995). Rane and colleagues have recently reported that the bolus intrathecal delivery of adenosine in human volunteers will reduce the areas of secondary allodynia after local skin inflammation and forearm ischemic pain ratings. (Rane, et al, 1998). At present there are no reports of chronic spinal delivery of adenosinergic agents in humans.
Cholinergic agonists
Preclinical studies on spinal activity

Intrathecal delivery of cholinergic agonists and acetylcholinesterase inhibitors results in antinociception in animals (Yaksh et al., 1985; Naguib and Yaksh, 1994; Gillberg et al., 1989; Smith et al., 1989; Abram and Winne, 1995; Abram and O'Connor, 1995). Early work suggested the importance of muscarinic receptors. Subsequent studies have also emphasized that spinally delivered nicotinic agonists can induce a potent pain behavior but this is also accompanied by a subsequent increase in nociceptive thresholds (Khan, et al, 1997; Damaj, et al, 1998). The spinal delivery of cholinesterase inhibitors have been shown to similarly increase nociceptive thresholds. Systematic examination of the spinal pharmacology of these actions emphasize the probable role of muscarinic M1 or M3 receptors.

Mechanisms of action
M3 binding sites have been localized in laminae I to III of the dorsal horn. M2 binding sites are present throughout the dorsal and ventral horns and background levels of M1 binding is noted. M4 binding has also been observed. (Hoglund AU; Bagdoyan, 1997). M1 binding has been shown in the chick dorsal root ganglia (Tata, et al, 1995). Recent studies have shown that Muscarinic receptors in dorsal horn can enhance GABA release (Baba, et al, 1998). These systems are likely complex. Others have shown that muscarinic agonists activity can also enhance nitric oxide release (Xu, et al, 1996). Electrophysiologically, muscarinic receptors appear to mediate a presynaptic inhibition which can regulate monosynaptic reflex activity (Yoshioka, et al, 1990).

Tolerance to the analgesic effect of cholinomimetics occurs rapidly in animal models of antinociception (Svensson et al., 1991).

Clinical utilization of spinal cholinesterase inhibitors

Intrathecal neostigmine (a acetylcholinesterase inhibitor) produces analgesia in humans (Hood et al., 1995; Lauretti and Lima, 1996). At doses that are analgesic in human volunteers, IT neostigmine is associated with nausea and vomiting and lower extremity weakness, as well as raises blood pressure and heart rate (Hood et al., 1995).

Gamma-amino butyric acid (GABA) agonists
Preclinical studies on spinal activity

While baclofen, a GABA-B agonist was early shown to have an antinociceptive effect when administered IT in several animal models (Wilson and Yaksh, 1978; Yaksh and Reddy, 1981), its therapeutic ratio as defined by the dose required to produce motor weakness is marginal. This potent effect upon motor horn function however is appropriate for its spinal delivery to treat spasticity in spinal cord injury and multiple sclerosis. There are also reports on the use of intrathecal GABA-A agonists for the management of pain (Borg, 1996).

Mechanisms of action

The GABAB receptor is a G-protein-coupled receptor. Activation of a GABAB receptor evokes a hyperpolarization of the membrane mediated by Gi protein coupled increase in potassium conductance, or a decrease in opening of voltage sensitive Ca2+ channels that serve to attenuate terminal transmitter release. (Bowery, 1993, Mott and Lewis, 1994). Receptor autoradiograph indicates that GABA-B site is found though out the spinal cord with the highest concentrations in the substantia gelatinosa. Unilateral rhizotomy and capsaicin treatment both reduced GABA-B binding, suggesting a location both pre and post synaptic to the primary
afferent. However, baclofen has no effect upon the spinal release of substance P, suggesting that its binding does not regulate that small afferent release (Sawynok, et al 1982; Go and Yaksh, 1987).

Clinical utilization of spinal baclofen

Although baclofen has been shown to have analgesic properties, the use of this drug for analgesic purposes is limited by the motor weakness it produces at analgesic levels. Because of this, it has been used mainly for the treatment of spinal cord spasticity which will not be discussed in this article. There are a few reports on the use of intrathecal baclofen both as a single agent and in combination with other drugs for chronic pain management (Middleton et al, 1996; Taira et al, 1995).

Combination Spinal Drug Therapies

There are several persuasive reasons to anticipate that codelivery of agents with distinct mechanism of action may be therapeutically advantageous. First, as indicated above and discussed in detail elsewhere (Yaksh, 1997a) many clinical pain states are a composite of several mechanism (e.g. acute afferent drive from the injury site, the persistent ongoing input that leads to a facilitated state and the central changes after nerve injury that leads to anomalous pain processing not dependent upon small afferent input). In such states, it is reasonable to presume that an agent with a defined mechanisms of action may include a component, but not all components of the systems that underlie the specific pain state. Second, there is strong evidence that the several agents may not display cross tolerance (e.g. µ and δ and µ and alpha 2 and attenuate the concurrent development of tolerance otherwise associated with an equipotent dose of a single when drug given alone. (Yaksh and Reddy, 1981). Finally, even for pain states that are mediated by the same mechanism, agents which act on different elements of the systems may display non linear interactions that enhance the therapeutic ratio. Numerous studies have emphasized that spinally delivered agents may show positively synergistic interactions as regards modulation of nociceptive processing. Some of these are summarized in Table 9. In the case for example of the interaction between spinal µ and alpha 2 agonists, an enhanced nociception can result without an attendant increasing respiratory depression or hypotension (see Yaksh and Malmberg, 1994).

Discussion on the question of efficacy of chronic spinal drugs.

Given the current literature on the efficacy of long-term intraspinal drug therapy, it is difficult to draw conclusions because of many deficiencies in these studies. First, none of these studies present the psychological assessment of the patients. It is well accepted that before embarking upon chronic intraspinal drug therapy, a psychological assessment should be performed. Often, psychological assessment can identify the patient who is destined for failure if ongoing counseling is not provided in conjunction with intraspinal drug therapy. Some patients will respond to psychological interventions alone.

Second, there is little mention of the methods used to screen patients for responsiveness to intraspinal drug therapy. This often involves either a single dose of drug intraspinally or a longer continuous infusion through an externalized catheter. The advantage of the continuous infusion is that it allows observation of the patients response in their own home environment which is quite different from that of a hospital or physicians office.

Third, there were no control groups, randomization, or blinding. Given, due to the expense and invasiveness of this therapy, it would be difficult to compare to a placebo infusion,
it is reasonable to attempt to compare intraspinal drug therapy to conventional methods. Also, it would be possible to blind a third person responsible for assessing outcome measurements. Future studies should be designed as single blinded, randomized, controlled studies comparing intraspinal drug therapy to conventional methods. Many national studies in cancer therapy have successfully used these methods.

Fourth, very few of the studies defined the pain syndrome of the patients. This is important as it is well known that neuropathic pain is less responsive to opioids than nociceptive pain. However, because of the multifactorial nature of many chronic pain conditions, it may be difficult to clearly categorize the pain. It may be easier to categorize pain by region (i.e. low back pain, extremity pain, abdominal, etc.).

Fifth, there is no standardization of the methods used to assess outcome. In fact, most studies are deficient in outcome measurements and rely only on changes in visual analog pain scores and fail to assess important aspects of outcome such as patient satisfaction, quality of life, and functional improvements. Future studies should use a standardized outcome measurement tool which is clearly defined. The new DIGIMED database may prove extremely valuable in this case.

Sixth, there are no standard protocols for selecting, increasing or changing the drug used for intraspinal drug therapy. Studies to date appear to choose at random the therapy and management of the therapy.

Finally, the studies to date are short to intermediate follow-up. It may be necessary to examine the outcome of this therapy for 5-10 years before solid conclusions can be made.

In all fairness, the criticisms of these studies are inherent to many studies on pain management outcomes. Chronic pain management is clearly very difficult to study due to the multifactorial nature. In general, the field of chronic pain therapy research is in need of properly designed prospective randomized trials.

**TOLERANCE AND INTRASPINAL DRUG DELIVERY**

In animal models, continued spinal infusion or repeated bolus delivery of an analgesically - effective dose of an opiate or alpha 2 agonist for an interval of 1-5 days typically displays: i) a reduction in the effect produced by a given dose of that drug; ii) an increase in the dose required to produce a given analgesic effect (e.g., a shift of the dose effect curve to the right and iii) a decreasing maximum response (Stevens and Yaksh, 1989). Experimental tolerance has several characteristics: i) There is typically little cross-tolerance between agents that act at separate receptors (e.g., µ vs δ; Russell, et al, 1987; Stevens and Yaksh, 1989; µ and α2: Stevens, et al, 1988; , Yaksh TL, Reddy, 1981); and ii) There is an asymmetric cross-tolerance between agents that act at the same receptor, but differ in intrinsic activity (see Paronis and Holtzman, 1992; Sosnowski and Yaksh, 1992).

Numerous mechanisms have been postulated for the development of tolerance. At present two interesting mechanisms that may prove relevant reflect the involvement of CCK pathways in the spinal cord and NMDA receptor activation. Intrathecal (Kellstein and Mayer, 1991) and systemic (Dourish, et al, 1990; Xu, et al, 1992) delivery of antagonists for the cholecystokinin B receptor have been shown to prevent the development of tolerance to opiates. While the intervening mechanism of this action is not certain, the general observations are consistent with the interpretation that CCK released at the spinal level may act in an “anti-opioid” capacity.

With regard to the NMDA receptor, it has been speculated that persistent opiate receptor occupancy may serve to phosphorylate the NMDA receptor (Chen and Huang, 1991) and this in
turns leads to increase phosphorylating activity of the opiate receptor that serves then to inactivate it. (Mao et al., 1995b). Accordingly, continuous co-spinal infusion or injection of an NMDA antagonist with a μ opiate (Dunbar, and Yaksh, 1997) or an alpha 2 adrenergic (Dunbar, and Yaksh, 1996) agonists will diminish the tolerance otherwise produced by that infusion. In recent work, we have shown that inhibition of spinal protein kinases C with intrathecally delivered PKC inhibitors will reverse over a 24 hr interval tolerance evoked by chronic opiate delivery (Granados-Soto and Yaksh, unpublished observations). It remains to be seen whether these mechanisms will impact upon the changes in response observed in the human pain patient, but they suggest exciting possibility for future development.

In humans, the spinal delivery of opiates for chronic pain is often accompanied by an incrementation over the period of infusion (Table 5). In a multicenter retrospective study in 163 cancer patients receiving continuous intrathecal infusion, an increase in mean infusion concentration was observed. During this interval, the variance of the data rose over time which reflected the ongoing reduction in group size at longer infusion intervals, and the finding that some patients showed significant increases while many others did not. This was particularly evident when the median and quartiles were plotted suggesting that the large majority of the population showed no further incrementation after the first months (see Figure 1). Plotting the individual incrementation in 33 patients over a 6 month period revealed that 21 of these patients displayed less than a 3 fold increase in starting dose. Such long term stability has been observed in a number of studies (Table 5).

![Histogram presenting the distribution of patient populations receiving intrathecal morphine infusion reported by the 19 physicians responding with usable information to the questionnaire.](image)

(From Yaksh and Onofrio, 1987; p. 216 fig 3)

While significant numbers of patients can achieve protracted pain relief with chronically delivered spinal drugs, it is clear that many (if not all) patients show some degree of dose incrementation. Several factors may account for such incrementation in clinical pain patients receiving continuous spinal drug therapy.

1. Pharmacokinetic changes. Abrupt return of pain in patients having achieved initial results from continuous intrathecal drug administration may result from changes in drug delivery or diffusion (see below under morbidity for details). These include: i) Withdrawal of the catheter from the epidural or subarachnoid space, ii) Development of a pseudomeningocele tracking along the course of the subcutaneous catheter from spine to pump, iii) Development of spinal
cord compression, iv) Miscalculation of the refill dose, v) Kinking or disconnection of the infusion catheter, vi) Change in catheter function. Epidural catheters have been shown to be invested in reactive tissue and this may lead to an altered level of spinal drug (see below under morbidity).

2. Change in pain intensity. Change in medical status (change in underlying pathology) may reflect changes in tumor mass/presence of metastasis or development of pain states incidental to primary pathology (bowel stasis; urinary retention; septic bladder / kidney). Progression of disease state may lead to the distribution of metastatic disease to previously unaffected dermatomes and by the invasion of organs which result in a more potent afferent pain stimulus (fascia/bone) resulting in an increased activation of the same C fiber evoked substrate. This results in a rightward shift in the analgesic dose response curve. Preclinical work has indicated that the degree of right shift will be inversely proportional to the intrinsic activity of the agonist. As stimulus intensity rises, the fraction of receptors that must be occupied is elevated and theoretically, the intensity of the stimulus may be such that at near full receptor occupancy, the agent will unable to block transmission (e.g. the agent becomes a partial agonist).

3. Changes in pain mechanisms. Preclinical models outlined above have demonstrated that different pain states may display a differential modulation by different classes of agents. Emergent pain states may result from nerve injury (e.g. developing tumors, radiation injury or chemotherapy). In such pain states, the aggravating stimulus may be the activation of a low threshold A-Beta fibers (Treede et al.1992), an input system which is less sensitive to opioids (Pierce and Brose, 1997). Several studies have suggested that dysesthetic pain states may show a comparatively poor response to opiates (Arner and Arner, 1988; Arner and Meyerson, 1988). In systematic studies, the efficacy of epidural morphine was found to rank: somatic > visceral > radiating pain. (Samuelsson and Hedner, 1991). Thus, emergent neuropathic pain states may result in the development of pain states sensitive to other agents, such as alpha 2 receptor agonists, or N type VSCC.

4. Pharmacodynamic changes (tolerance). Continued exposure to drugs such as opiates has been shown to result in a reduction in the responsiveness to the agent. This phenomena in spinal drug delivery models is not believed to be secondary to decreased concentrations (e.g. increased metabolism or clearance). Continued exposure results in a right shift in the dose effect curve with a decreasing maximum, a property suggestive of a reduction in receptor number.

5. Change in psychosocial status. Evolution of pain states are frequently accompanied by significant changes in emotional status and the development of principle states of depression and changes in life style and coping mechanisms must be considered when significant changes in treatment efficacy are observed.

SAFETY EVALUATION OF SPINALLY DELIVERED AGENTS.

Current insight into pain processing has provided ample insight that many components of the pain state may be encoded at the spinal levels and that these several mechanisms possess distinct pharmacology. Importantly, the preclinical animal models have been proven to be reasonably good predictors of the efficacy of these agents in several human pain states. This differential pharmacology and evidence of efficacy leads naturally to the impetus to employ these agents in humans. As in animal models, the therapeutic activity of the agent, even if it is active by a systemic route of delivery, may be enhanced by spinal delivery. Such implementation in humans, however, must be preceded by the systematic demonstration in preclinical models of the safety of the agent when given by that route. Several properties of an
appropriate safety evaluation include: i) a well defined chronically catheterized animal model with delivery into the space (epidural or intrathecal) anticipated for human use; ii) long term exposure (either repeated bolus or continuous infusion); iii) concentrations which at least equal and preferably exceed that which will be employed in humans by that route; documentation of effects upon behavioral (motor and sensory function), physiology (cardiovascular; spinal cord blood flow) and histopathology of the spinal cord, and roots. An extensive discussion of safety evaluation for spinally delivered drugs can be found elsewhere (Yaksh and Malkmus, 1999; Yaksh, et al, 1999) Table 10, presents a summary of data generated in a single model for several classes of agents that have been widely employed. The importance of the appropriate robust investigation of safety cannot be minimized. The observation that lidocaine produces a concentration dependent neurotoxicity in humans after intrathecal delivery is an important example as to how drug concentrations (as opposed to dose) and delivery protocol (microprobe versus injection by bolus and barbatoge) can influence the safety of even a widely used spinal agent. (Rigler, et al, 1991). In the case of preclinical safety evaluations, the information generated must always be considered from a conservative perspective. The assertion of safety garnered from a preclinical study cannot extend beyond the envelope of the study dosing and concentrations. Moreover, to the degree that the humans dosing approaches that examined in the preclinical model, the margin of certainty suggested by the preclinical study is reduced.

### Table 10. Summary of Relative Bolus Exposure Studies for Spinal Agents in Dogs Versus Those Concentrations Used in Humans

<table>
<thead>
<tr>
<th>Spinal Drug</th>
<th>Max Test Conc. (dog)</th>
<th>Clinically Used Concentrations</th>
<th>Relative Exposure Factor*</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine-bolus-IT</td>
<td>20 mg/mL</td>
<td>2 mg/mL</td>
<td>30.1</td>
<td>Sabbe et al., 1994 (D)</td>
</tr>
<tr>
<td>Sufentanil-bolus-IT</td>
<td>100 µg/mL</td>
<td>5 µg/mL</td>
<td>60.1</td>
<td>Sabbe et al., 1994 (D)</td>
</tr>
<tr>
<td>Neostigmin-infusion-IT</td>
<td>1.000 µg/mL</td>
<td>125 µg/mL</td>
<td>24.1</td>
<td>Henschel et al., 1991</td>
</tr>
<tr>
<td>Bicarbonate-infusion-IT</td>
<td>2.000 µg/mL</td>
<td>200 µg/mL</td>
<td>30.1</td>
<td>Yaksh et al., 1985 (D)</td>
</tr>
<tr>
<td>Cocaine-infusion-EP</td>
<td>2.000 µg/mL</td>
<td>70 µg/mL</td>
<td>66.1</td>
<td>Kisely et al., 1986 (D)</td>
</tr>
</tbody>
</table>

*Conc in dog/Conc in human x estimated exposure factor. The larger the number the greater is the estimated acute exposure in the dog after a bolus delivery.

Abbreviations: D, dog; H, human; E, daily bolus; T, continuous infusion.

INTRASPINAL DRUG DELIVERY TECHNIQUES

There are basically three types of intraspinal delivery techniques: 1) externalized system; 2) partially externalized system; and 3) totally implanted system. Each technique has different risks and costs which are taken into account when deciding which approach to use. Parameters of drug delivery, e.g. infusion rates and bolus injection volumes depend on a variety of factors.

**Externalized systems**

The externalized epidural catheters are the most widely used techniques for delivering drugs to the perispinal space. Such systems are designed for short-term (hours to days) use, but have been successfully used for longer term delivery (weeks to months). The use of an externalized catheter leads to possible concern that the catheter will develop a local infection at the exit site and that the catheter may serve as a favorable access track for either epidural or intrathecal infection. Because of the potential risk of infection, extended placement of externalized systems are usually reserved for the epidural route only. In the terminally ill patient, the risk: benefit ratio may be that the intrathecal route is justified with an externalized
The incidence of infection is reviewed below. Some practitioners tunnel these catheters under the skin for some distance to provide stability and reduce the likelihood of inadvertent withdrawal.

There is currently only one FDA approved externalized intrathecal delivery system, the Algoline Intraspinal Catheter. This catheter is made of silicone and is closed tip with lateral eyes. The Algoline is the most logical choice since it is FDA approved for intrathecal placement; however, any of the catheters described above may be used. If an intrathecal externalized system is used, great care must be used to prevent infection. Logically, the less the catheter is manipulated, the less chance of infection (DuPen, 1995).

The externalization clearly provides a chronic breach of the cutaneous barrier. To minimize the risk of infection, strict aseptic techniques should be used when handling these systems. In addition, catheters may be prepared with cuffs which can enhance the local formation of scar tissue to minimize bacterial tracking. Extensive work with percutaneous catheters for parenteral drug delivery as in cancer patients led to the development of the Hickman catheter which possesses a Dacron cuff for antimicrobial protection. Epidural catheters for chronic placement, such as the DuPen, Algoline (Medtronics Inc), SKY (PMT, Inc), and E-Cath catheter have such fittings. Dacron cuffs at the exit site are believed to minimize catheter site and catheter related infection risk. The Dacron cuff also results in catheter anchorage to the subcutaneous tissue at the exit site.

The longer the externalized system is used, the greater the risk of infection. The infection usually occurs from bacteria tracking along the catheter at the insertion site. Infections that reach the epidural or intrathecal space can be very serious and even lead to paraplegia. This risk is lessened if the catheter is tunneled subcutaneously to exit the skin at a distance from the actual entrance into the intraspinal space; however, this has been challenged (discussed below). If the catheter is to be left in place for more than 7-10 days, it is recommended that it be tunneled. If the catheter is to be used for more than 6 months, it is recommended that a totally implanted system be used (see below).

**Partially externalized systems**

Partially externalized systems are those in which the catheter is placed by a needle inserted into the target site though a small incision of the skin. The external end of the catheter is then connected to an access port which is placed under the skin. The port is secured by suture loops. The incision is then sutured closed. Injections are made by placing a needle though the skin and into the access port (DeJong and Kansen, 1994; Cherry et al, 1985). The Port-a-Cath epidural port system (Pharmacia-Deltec, Inc., St. Paul, MN) is the only FDA approved implanted port system (figure 2). It is a silicone open tip (no lateral eyes) catheter with an implanted subcutaneous access port.

While it is clear that the subcutaneous systems permits freedom of movement and reduces the risk of catheter removal and eases the impediment to patient movement, it may be asked as to whether the use of the subcutaneous port confers any safety benefit as compared to a well maintained percutaneous system. A study by
deJong and Kansen considered the infection rate of three epidural catheter techniques: i) subcutaneous port, ii) non tunneled externalized or iii) a tunneled externalized catheter (DeJong and Kansen, 1994). They concluded that when the infection rate was indexed to catheter-days, the number of infections per 1000 catheter-days in the injection port group was half that of the percutaneous group (2.86 infections versus 5.97 for percutaneous catheters). No injection port became infected during the first 70 days of treatment, whereas in the percutaneous group infections occurred as early as the first week. Another study showed no infections in 252 patients using the subcutaneous port system (Liew and Hui, 1989). From these study, it appears that subcutaneous port systems are superior to externalized systems if long term use is anticipated. As with the externalized systems, there are no currently approved partially externalized systems for intrathecal use. However, the Port-a-Cath system has been successfully used for intrathecal drug delivery.

**Totally implanted systems**

Totally implanted systems are those with the catheter and delivery system completely implanted (Figure 3). They have the advantage of a lower risk of infection and allowing the patient more independence. The totally implanted systems are more expensive and requires a greater surgical intervention than the externalized or partially externalized systems. Accordingly, the patients should be carefully selected. These systems are generally reserved for patients with a life-expectancy of greater than one year although some physicians have routinely decreased this to six months (see below under economics). In 1981, the first intrathecal pump was implanted for the delivery of morphine in the treatment of chronic intractable pain (Onofrio, et al, 1981) using an Infusaid pump systems. Soon thereafter, the Medtronics pump was approved and became available for the delivery of baclofen in the treatment of spasticity (Penn and Kroin, 1985). The FDA released this pump to the market in 1991 and is now marketed as the commonly known Synchromed Infusion Pump (Medtronic Inc., Minneapolis, MN).

There are currently three approved commercially available devices and two in clinical trials. The current FDA approved systems include the Synchromed Infusion System, Arrow Constant Flow Implantable System (Arrow Int., Reading PA), and Infusaid System (Pfizer, Norwood, MA). These systems are accessed percutaneously for pump refills. Pump refills are required at intervals depending on the infusion rates and the size of the pump reservoir. All three pumps have direct access ports to the cerebrospinal fluid for bolusing or aspiration. The infusion systems are implanted in the lower abdominal subcutaneous fat and connected to a catheter which is tunneled subcutaneously around the abdominal wall into the cerebrospinal fluid (CSF) (Krames, 1996; Penn et al, 1995).
Pump systems

Pumps may be classified according to their mechanism of delivery; programmability; delivery rates and reservoir volumes. Table 11 summarizes the features of these pumps.

An additional consideration is the drug for which the pump is approved. There are two issues. First, the device is approved for a given material by the FDA. This reflects upon the product label of the solution which is to be infused and reflects upon the safety of the product given by continuous infusion at certain concentrations. The second issue reflects upon the compatibility of a drug or a drug mixture for each pump model. These devices have a variety of metals (typically titanium or stainless steel), perfluorocarbon seals, methocelulose filters and a variety of catheter materials. Compatibility may reflect upon the possibility of i) chemical interactions which are deleterious to the pump reservoir or to the pumping mechanisms; ii) altered solubility because of a drug mixture or some interaction specific to the materials in the pump. An example is meperidine which has been suggested by the manufacturer of the Synchromed Infusion System (Medtronic, Inc.) that this agent may be incompatible with the pump. This is secondary to the pH of the drug which may lead to corrosion of the internal pump tubing. In addition, there is a tendency for high concentrations to be employed in an effort to increase the refill interval. Such concentrations may approach the limit of solubility of the drug alone or the drug combination which may lead to precipitation within the implanted device, rendering it inoperative. Close consultation with the manufacturer must be undertaken before implementation of high concentrations or unusual combinations.

Table 11. Comparison of Implantable Devices for Intrathecal Drug Delivery

<table>
<thead>
<tr>
<th>Material</th>
<th>SIS</th>
<th>ACFIS</th>
<th>IS</th>
<th>IsoMed</th>
<th>Alomed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septum diameter</td>
<td>6 center</td>
<td>12 center</td>
<td>8 center</td>
<td>12 center</td>
<td>12 center</td>
</tr>
<tr>
<td>(mm)</td>
<td>6.0</td>
<td>12.0</td>
<td>8.0</td>
<td>12.0</td>
<td>12.0</td>
</tr>
<tr>
<td>Weight (g)</td>
<td>205</td>
<td>208</td>
<td>208</td>
<td>208</td>
<td>208</td>
</tr>
<tr>
<td>Height (mm)</td>
<td>27.5</td>
<td>28</td>
<td>28</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>Diameter (mm)</td>
<td>85.2</td>
<td>87</td>
<td>87</td>
<td>87</td>
<td>87</td>
</tr>
<tr>
<td>Reservoir volume</td>
<td>10 and 18</td>
<td>50</td>
<td>20</td>
<td>20, 35, and 60</td>
<td>50</td>
</tr>
<tr>
<td>(mL)</td>
<td></td>
<td></td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Flow rates</td>
<td>Programmable</td>
<td>Preset, (mL/h)</td>
<td>Preset</td>
<td>Preset, (mL/h)</td>
<td>1 mL/h maximum</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.5-0.85 Low</td>
<td>1.0-5.0/d</td>
<td>0.5 Low</td>
<td>1.0 Medium</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.85-1.45 Medium</td>
<td></td>
<td>1.5 Medium</td>
<td>1.5 High</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.45-2.0, high</td>
<td></td>
<td>2.0, high</td>
<td>2.0, high</td>
</tr>
<tr>
<td>Power supply</td>
<td>Battery, multi-step bolus, continuous, continuous complex, bolus delay</td>
<td>Freon Constant flow</td>
<td>Freon Constant flow</td>
<td>Frigon R-114 Constant flow</td>
<td>Manually activated Patient activated</td>
</tr>
<tr>
<td>Infusion modes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septum puncture</td>
<td>500 punctures</td>
<td>1,500 punctures</td>
<td>1,000 punctures</td>
<td>1,000 fill port</td>
<td>&gt;2.5 yr</td>
</tr>
<tr>
<td>life</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>List price</td>
<td>$7,325.00 Pump, $6,500.00 Programmer</td>
<td>$4,995.00</td>
<td>$4,995.00</td>
<td>$4,995.00</td>
<td>$4,995.00</td>
</tr>
</tbody>
</table>

Abbreviations: SIS, SynchroMed Infusion System; ACFIS, Arrow Continuous Flow Infusion System; IS, Infusaid System.

The Synchromed Infusion System (SIS) is the only implantable pump that is programmable (figure 4 and 5). The pump is programmed externally through a radio-telemetry link. The programmability allows for a variety of infusion modes which includes continuous infusion, continuous-complex infusion (increases and decreases throughout the day), single bolus, and intermittent bolus. The SIS is intermediate in weight between the Arrow and the Infusaid pump. It comes in two models, one with a 10 ml and one with an 18 ml reservoir. These reservoir volumes are smaller than the other two pumps but because of the extremely low flow rates that can be achieved, pump refills may only be required up to 60 days. It also has the lowest septum puncture life (500 punctures) but this is considered to be less of a problem.
because of the lessened need for repeated punctures due to the programmability. Battery life is from 3-5 years after which the pump must be removed and replaced. The SIS is approved for intrathecal morphine and baclofen.

The Arrow Continuous Flow Infusion System (ACFIS) is the newest pump on the market (figure 6). It is only approved for intrathecal morphine. This pump is not programmable and has a factory preset flow rate (low, medium, and high). The flow rate is controlled by a flow restrictor which controls the flow rate based on the drug viscosity. Therefore, flow rates may vary for different drugs based on differences in viscosity. A significant increase in drug viscosity may occur with very high concentrations thus impairing flow rate (For example the flow rate for water in a medium flow pump is 1.1 ml/day and for morphine sulfate it is 1.0 ml/day) (Rippe et al, 1984). In addition, changes in body temperature and atmospheric pressure will change flow rate by affecting the gas pressure within the system. Because of the non-programmability, in order to increase the amount of drug delivered, the pump must be refilled with a higher or lower drug concentration. This usually results in more frequent pump accessing in the beginning. The infusion is driven by freon therefore it does not require replacement as does the SIS. The pump is available in two reservoir volumes of 16 ml and 30 ml. It has the highest septum puncture life (1500 punctures) and is similar in weight and size to the IsoMed Infusion System (discussed below). Whereas the SIS and the Infusaid System have a direct access side port to the CSF separate from the pump refill access port, the ACFIS direct CSF and pump refill port are accessed through the same septum. There is a built in safety mechanism which prevents direct injection into the CSF when filling the pump (figure 7). This is an advantage over the SIS and the Infusaid System since one can accidentally access the side port while filling the pump and result in an overdose. However, this is highly unlikely since the side port is some distance from refill port. In addition, pump refills use a 22 gauge needle and the CSF side port requires a 25 gauge needle for entry thus providing an additional safety mechanism.
The Infusaid System is a reliable device similar to the ACFIS (figure 6 and 8). Differences include larger size and weight, larger reservoir volume, pre-set flow rate between 1-5 mL/day, and lower septum puncture life (1000 punctures). The larger weight and size is a disadvantage as compared to the ACFIS. The ACFIS has largely replaced the Infusaid System in clinical practice.
There is one constant flow rate infusion system in clinical trials. The IsoMed Infusion System (Medtronic Inc., Minneapolis, MN) is similar to the ACFIS in all aspects except it has a CSF access port separate from the central reservoir fill port. As with the SIS, the CSF side port requires a 25 gauge needle for access. The pump is available in three factory preset flow rates of 0.5, 1.0, or 1.5 ml/day. It is also available in three reservoir sizes, 20 ml, 35 ml, and 60 ml (figure 9 and 10).

There is one patient-activated system in clinical trials. The Algomed Model 84112 Infusion System is an implanted delivery system designed to provide patient-controlled, intermittent bolus injection of drugs into the intrathecal space (figure 11). The system is activated by finger pressure on a control pad underneath the skin. The system allows up to 1ml/hour to be delivered. It is anticipated that the system will soon be available for the delivery of morphine. The system includes the reservoir, control pad, catheter (figure 12). The control pad consists of three components: a reservoir fill port, a pumping chamber and activation valve (figure 13). The pumping chamber has a maximum volume of 1 mL and limits the amount of drug that can be delivered. The pumping chamber must be depressed at the same time as the activation valve in order to deliver a bolus. Following the bolus, the pumping chamber slowly fills over sixty to ninety minutes. The catheter is made of radiopaque silicone rubber.
MORBIDITY OF CHRONICALLY IMPLANTED SYSTEMS

In general, the morbidity from intraspinal drug delivery is uncommon although the risk of infection is more common with the external systems as opposed to the totally implanted systems. The morbidity can be divided into those associated with the drug delivered (as discussed above), those associated with the catheter system, those with the pump or port pocket, and pump system complications.

Catheter associated morbidity

The most serious morbidity of intraspinal catheterization are related to the catheter system. These complications include neurological complications secondary to the catheter or epidural fibrosis, catheter infection, catheter fibrosis/inflammation leading to pain on injection, obstruction and altered diffusion kinetics of the drugs delivered, and catheter malfunction.

Neurologic complications

Neurological complications from placement of an epidural or intrathecal catheter is a rare occurrence. Most severe neurological complications from epidural catheterization occur from an epidural abscess or epidural fibrosis. Even these are rare occurrences. Both of these phenomenon are discussed below. Transient neurologic abnormalities following lumbar epidural blockade are much more common than permanent abnormalities (0.1% vs 0.02% respectively) (Dawkins, 1969; Usubiaga, 1975). There have been reports of paralysis associated with epidural anesthesia in the presence of spinal stenosis (Skoven et al, 1985; Yuen et al, 1995). The mechanism of nerve injury in spinal stenosis may be secondary to the injection of fluid into a space of limited volume, or the development of edema resulting in acute compression of the cauda equina at the level of the stenosis (Yuen et al, 1995).

Infection

Catheter infection represents a potentially serious but infrequent complication of intraspinal catheterization. It is most common with externalized long-term catheters and patients who are immunosuppressed (Linnemann and Bulow, 1993). With long-term catheters, the incidence of catheter insertion site infection is higher than actual nervous system infection (4.3 vs <1%) (Holt et al, 1995; Pegues et al, 1994; Du Pen et al, 1990; Aguilar et al, 1992; Yue et al, 1991; Erdine and Aldemir, 1991; Bauer et al, 1979; Hicks et al, 1994; Byers et al, 1995).

The incidence of infection in short term (< 1 week) catheters is extremely low (Nickels et al, 1989)( Bevacqua et al, 1994). There does not appear to be any differences in catheter infection rates of epidural vs intrathecal catheters (Nitescu P et al, 1995). Infections may involve mild catheter colonization, deep paraspinous muscle infections, clinical meningitis, or epidural abscess. The catheter hub is regarded as the main point of entry of bacteria leading to catheter colonization; however, hematogenous spread and tracking of bacteria from the insertion site may also occur. The most common microorganisms that have been isolated from intraspinal catheters include coagulase-negative staphylococci, Staphylococcus aureus, Gram-negative bacilli. Gram-negative bacilli and S. aureus tend to cause more serious infections.

Although rare, case reports of epidural abscesses have been made with long-term epidural catheters (Linnemann and Bulow, 1993; Kobayashi et al, 1993; Sollmann et al, 1987; Strong, 1991). Stappylococcus aureus is the most common bacteria isolated from epidural abscesses followed by gram negative rods. Rare organisms include mycobacterium, brucella, actinomycoses, other fungi, echimiococcus, and the Guinea worm. Whether epidural infection is through hematogenous spread or through the catheter hub is controversial. It is believed that the initial step in hematogenous spread is minor trauma to the epidural fat leading to fat necrosis.
The necrosed fat does not resist the infection and will seed bacteria from the blood during transient bacteremia (Hartstein and Robles, 1988; Browder and Meyers, 1937). However, even in the presence of infection, epidural catheters have been shown to be safe. Jakobsen and colleagues reported a series of 69 patients who required an epidural catheter for repeated surgical treatments for abscesses or infected wound. Twelve patients had their epidural catheters removed because of signs of local infections but there were not serious infections. The authors concluded that epidural catheters are relatively safe in this patient population (Jakobsen et al, 1995). These situations should be evaluated on a case by case basis.

If there is the possibility of immunosuppression or poor wound healing (i.e. AIDS, diabetes) it is not recommended that a catheter be used. If an epidural abscess is not diagnosed early, it may lead to paralysis. However, if there are no neurological symptoms of the abscess, it may be possible to treat nonsurgically with antibiotics (Kobayashi et al, 1993). There is one case report of an infected long-term epidural catheter being sterilized in vivo with intravenous antibiotics (Hahn et al, 1992). There is also a case report of a patient who developed staphylococcal meningitis after an intrathecal synchromed infusion pump implantation. The meningitis was successfully treated with intrathecal vancomycin via the implanted pump (Bennett et al, 1994).

Patient selection and strict aseptic technique are the most important factors in preventing catheter infection. As mentioned above, caution should be exercised when using intraspinal catheters in the immunocompromised or diabetic patient. Other methods that may be used to prevent catheter infection include antimicrobial dressings and the use of bacterial filters. Shapiro et al showed a significant reduction in catheter colonization when using a chlorhexidine dressing (Shapiro et al, 1990). Bacterial filters have been advocated to reduce infection rates. However, De Cicco et al demonstrated a higher incidence of catheter hub colonization if the bacterial filters were changed too often. They concluded that these filters maintain function for at least 60 days and should not be changed infrequently (De Cicco et al, 1995). Intermittent epidural aspiration should only be done if an infection is suspected. Frequent aspiration to monitor the presence of an infection may only lead to an increased risk of contamination. Tunneling the catheter subcutaneously to exit at a site distant from the needle puncture site has been advised to reduce the incidence of catheter infection. This recommendation is based on the assumption that catheter colonization and intraspinal infections occur from the bacteria tracking along the catheter. However, studies have not supported this assumption and only show that tunneling will reduce the incidence of catheter dislodgement and not catheter infection (Byers et al, 1995; de Jong and Kansen, 1994). It has been suggested that local anesthetics are bacteriocidal and may prevent catheter infection; however, the concentrations commonly used probably have no effect (Feldman et al, 1994)( James et al, 1976)

Catheter fibrosis/inflammation

Over time, both intrathecal and epidural catheters can become difficult to inject and cause pain on injection (Driessen et al, 1989; Arner et al, 1988; Du Pen et al, 1987; Liew and Hui, 1989; Shigihara et al, 1995). As reviewed in Chapter 12, foreign bodies placed within the epidural and intrathecal space can induce some degree of local reactivity. The nature and magnitude of the reaction may depend upon the catheter material (see Chapter 16), but in this regard considerable work remains to be accomplished.

The local reaction can have two consequences. First fibrosis can potentially become a space occupying intrusion into the respective space. Secondly, the fibrosis may result in altered diffusion kinetics of the drugs delivered in the epidural and intrathecal space may develop (Samuelsson et al, 1987; Shigihara et al, 1995).
Epidural catheters. It is the common conclusion that a local reaction to the catheter may cause the above observations. Animal studies have shown the development of a fibrous sheath around epidural catheters which occur as early as 7-10 days (Durant and Yaksh, 1986; Sabbe et al, 1994; Coombs et al, 1994; Coombs et al, 1994; see Chapters 13 and 16). In man, studies have shown catheter encasement (Carl et al, 1983; Cherry and Gourlay, 1992; Aldrete, 1995) to the point of requiring surgical correction due to spinal cord compression (Rodan et al, 1985; North et al, 1991). One study showed an 11.6% incidence of back leakage from the insertion point with long-term catheters (Auld et al, 1985). The incidence of epidural fibrosis secondary to a catheter appears to be between 0.5-19% (Driessen et al, 1989; Arner et al, 1988; DuPen et al, 1987; Aldrete, 1995). Epidurograms in patients with epidural fibrosis secondary to a catheter shows encapsulation at the catheter tip (Arner et al, 1988; Cherry and Gourlay, 1992). One study on intrathecal catheters showed a 9.5% incidence of fibrosis (Penn et al, 1995).

Review of the literature shows a comparable epidural reaction to the catheter across species. The time course of epidural reactions are typically reported to be around 10 days for the rats (Durant and Yaksh, 1986), 7-14 days for dogs (Sabbe et al, 1994), 30 days for sheep (Coombs et al, 1994) and 1-2 weeks for humans (Hogan, 1993; Takahashi et al, 1991; Nagaro, 1986; Shihigara et al, 1995). In general, the observed tissue reactions in the epidural space of dogs are similar to those occurring in response to foreign materials in other tissues: intravascular catheters and pacemakers, subcutaneous tissue, the mammary area, and intraperitoneal area. Studies on long-term epidural catheter histopathology describe a nonspecific inflammation at the tissue-implant interface that is initially acute and progresses to a predominately chronic inflammation and eventually encapsulation. This reaction occurs most commonly at the tip where biomechanical stresses are the most (See Chapter 13).

There have been several studies on postmortem morphological changes that have been demonstrated in humans. Ehring and Boekstegers looked at the morphological changes in the epidural space of a patient who received a 114 day infusion through a nylon epidural catheter (Perifix catheter, Braun Medical Inc., Bethlehem, PA) for cancer pain management. No macroscopical or histological indication of inflammation could be observed in any of the peridural space and spinal canal. The only alterations detected were nonspecific foreign-body reactions, such as an increase in foreign-body giant cells and single connective tissue adhesions (Ehring and Boekstegers, 1989). This is consistent with a report on 15 patients who had chronic epidural or intrathecal morphine via a nylon catheter for intractable pain. There was no reaction against the nylon catheter nor was there any neuropathologic findings related to the duration or cumulative dose of the intrathecal treatment. No new neurologic deficits could be attributed to the intrathecal administration of the opiate-bupivacaine mixtures. The authors concluded that the neuropathologic and clinical neurologic findings in cancer patients treated with intrathecal morphine-bupivacaine mixtures appeared similar to those in animals and humans reported with either intrathecal morphine or bupivacaine alone (Sjoberg et al, 1992). Although human autopsy reports have failed to demonstrate significant reactions to agents delivered in the epidural space there are several reports in animals to the contrary. Larsen et al demonstrated that morphine causes a significant inflammatory reaction in goats after epidural administration (Larsen et al, 1986). This is important because epidural and intrathecal reactions to various agents may be species specific and caution must be used when interpreting data from preclinical toxicology studies.

Intrathecal catheters. Epidural reactivity has been more extensively studied than intrathecal reactivity and the properties of the epidural space cannot necessarily be extended into the intrathecal space. Crul and Delhass looked at the differences in complications with cancer patients requiring epidural and intrathecal catheters for pain control. During the first 20 days of
treatment, a significant difference in the incidence of complications was observed between the epidural group (8%) and the subarachnoid group (25%). During the remainder of the treatment period the complication rate rose to 55% in patients receiving epidural morphine and declined to 5% in the subarachnoid group, a significant difference. The most frequent complication in the epidural group was obstruction and dislocation of the catheter, probably due to the development of epidural fibrosis. The most frequent complication in patients with an intrathecal catheter was CSF leak in the first two weeks. The authors concluded that the subarachnoid route is preferred for patients expected to live longer than one month (Crul and Delhass, 1991).

Factors which influence local reactivity include the space (epidural versus intrathecal); catheter properties (net charge, smoothness, wetability, the possibility of outgassing of volatile agents used in sterilization, biomechanical factors and susceptibility to infection. (See Chapter 16, for a more extended discussion). Occult infection has been hypothesized to be a cause of encasement and capsular contracture of silicone breast prostheses. It has been demonstrated that breast prostheses soaked in a 50-50 mixture of an iodine and saline solution as well as irrigating the wound with this solution decreases occult infection (Landon et al, 1993; Virden et al, 1992). There have been no studies on the use of iodine solutions to sterilize intraspinal catheters.

In summary, epidural fibrosis continues to be a minor problem in long-term catheterization. Most patients can achieve long-term catheterization without significant fibrosis and altered drug delivery. The reactivity appears to be less in the intrathecal space allowing for much more prolonged drug delivery.

**Catheter malfunction**

Previous studies of intrathecal delivery systems have found catheter malfunction occurring at rates varying from 10%-40% (Penn et al, 1995). Catheter malfunction can be divided into the following categories: 1) disconnection from the pump or port, 2) large to small catheter disconnect (if present), 3) kinks or holes in the catheter, 4) catheter breaks, and 5) catheter dislodgements. The implantable infusion pumps have two locations where the catheter may become disconnected, from the pump or port, or from the large to small catheter disconnect. Over time, the catheters may develop a kink or hole and may also break anywhere along the catheter. Penn et al performed a prospective study of a thin and thick walled intrathecal catheter reliability in 102 patients. Sixty percent of the patients had no catheter complications; the remaining patients had one to five complications. Most of the complications occurred in the thin walled silastic catheter and the authors concluded that the thin-walled silastic catheter does not perform well and the larger, thick-walled catheters should be used. Presently, most of the catheter in use are thick walled.

**Pump or port pocket associated problems**

Complications that can occur in the pocket include hematoma, seroma, infection, and capsule formation. Hematomas usually occur immediately postoperatively. Meticulous care should be taken to control all bleeding prior to surgical incision closure as the development of a hematoma provides a nidus for infection and the pocket may require surgical exploration to evacuate the hematoma. Hematomas can be prevented by appropriately screening the patients for coagulopathies prior to pump implantation.

Seromas may also develop around the pump or port. As with hematomas, seromas may also increase the chances of infection in the presence of a foreign body. If the patient develops a seroma, it can be drained percutaneously taking care to use strict aseptic technique. Seromas can be prevented by requiring the patient to wear an abdominal binder for one month after the implantation.
Infections may occur in the pump pocket or back incision. Not all wound infections require pump or catheter removal and if superficial, it can be treated with antibiotics. If an infection of the pocket is suspected, careful aspiration is useful to provide a culture and sensitivity. If the infection is deep and severe (associated with fever and leukocytosis), the system should be removed. It may be necessary to leave the wound open in this case and allowed to close secondarily. Consultation with an infectious disease specialist may be helpful.

As with any foreign object, the body will usually form a fibrous capsule around the object. With silicone breast implants, this often leads to capsular contraction and pain (Wallace et al, 1996). This may also occur with implanted pumps or ports and the patient may complain of pain. This rarely requires intervention, however, some patients may require the system to be removed if the pain becomes severe.

**Pump system associated problems**

Programmable pump complications can be divided into filling errors, pump failure, programming errors, and torsion or flipping of a freely moveable pump (Krames and Schuchard, 1995). Complication that can occur when filling the pump include inadvertent side port access, overfilling the pump, and inadvertent placement of drug in the pump pocket. Many of the intrathecal pumps contain a side port with direct access to the intrathecal space. If this side port is inadvertently accessed when refilling the pump, a large dose of medication will be delivered directly into the CSF leading to a drug overdose. The Synchromed 8615 and 8615-S pumps and the Infusaid model 400 pump contains side ports. The Synchromed 8615-S pump has a screened side port which will only allow entry of a 25 gauge needle. This will prevent access from the usual 22 gauge huber type needle used for pump refill. Also the side ports are located on the periphery of the pump whereas the refill port is located in the center. The refill kits contain a template which can be used to locate the two different ports. The Arrow model 3000 pump has a special bolus needle for bolus injections directly into the CSF. The needle is designed with a sealed tip and a slot opening mid-way up the needle cannula. When the needle is inserted through the double stacked pump septums within the pump, the closed tip is in contact with the needle stop and the slot opening is automatically at the level of the bolus pathway allowing bolus injection or infusion (figure 6). If the pump is overfilled, the reservoir will be overpressurized which may lead to pump damage, failure, or overdose. Most pumps come with a manometer system to alert the physician or nurse of an overpressurized system. If the pump or port pocket is inadvertently accessed and the drug deposited directly into the pocket, a drug overdose can result. Most of the drugs used for intrathecal drug delivery are highly concentrated and can lead to very high plasma levels and drug overdose.

Pump failure most often occurs with battery failure. The Synchromed Infusion System is the only system that is battery operated. The normal battery life depends on the flow rate but is usually 3-5 years. The pump has a battery alarm that will alert the patient and physician when the battery is getting low. When the battery fails, the entire pump must be replaced. By the time the battery requires replacement, most patients are on a stable flow rate and do not require many rate changes. At this point it is may be more cost effective to use one of the constant flow rate systems (Arrow or Infusaid) that are not battery operated. These systems are also less expensive than the Synchromed Pump. However, these systems also have disadvantages unique from the Synchromed Pump (as discussed above) which should be weighed. Another cause of pump failure is failure of the electronic telemetric receiving module which prevents the pump from receiving programming instructions. This converts the pump to a constant flow system (like the Arrow and Infusaid Systems). If the patient is at a stage where programmability is not
important, the pump may be left in and adjustments in drug dosing made by changing drug concentration.

Programming errors can lead to inadequate pain relief, abstinence syndrome or drug overdose. Programming a drug concentration that is higher than the actual drug concentration may lead to underdosing and increased pain or drug abstinence syndrome. Programming a drug concentration that is lower than the actual drug concentration may lead to drug overdose and death. The newer software that is available with Medtronic programmable pumps asks the programmer if the right choices have been made which the programmer should carefully check. Also, the software has certain constraints which do not allow extreme changes in drug concentration or rates.

Pumps or ports that are not secured with sutures inside the pocket can flip or torque. Pumps that torque within the pocket may kink the catheter or pull the catheter out of the intrathecal space. If the pump flips on itself, the pump will be unable to be refilled or programmed. This problem usually is discovered at the time of refill when the pump cannot be accessed or programmed. If this happens, the pump will require surgical revision. The pumps and ports have anchors that can be sutured in the pocket thus preventing this complication.

PATIENT SELECTION

Patient selection for chronic intraspinal drug administration requires a careful evaluation of the patient. The decision to embark on this technique must not be taken lightly and the patient must be motivated enough to participate in their care plan and be responsible. There are slightly different selection criteria for malignant pain versus non-malignant pain as summarized in Table 12. Objective evidence of pathology is more important for non-malignant pain than for malignant pain because of psychological issues that surround pain of unknown etiology. It is not to say that patients without objective evidence of pathology should be excluded, rather they should be evaluated closely for psychological issues (discussed below). If they are declared psychologically stable for implantation, then one should proceed even in the absence of objective pathology. Another difference is that a life expectancy of greater than 3 months for malignant pain is important because of the costs of this technique (discussed below). Once the patient is declared a candidate for long-term intraspinal drug administration, a thorough screening trial is necessary.

<table>
<thead>
<tr>
<th>Table 12: Selection Criteria for Long-term Intraspinal Drug Administration</th>
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<tbody>
<tr>
<td>Malignant pain</td>
</tr>
<tr>
<td>Life expectancy &gt;3 mo</td>
</tr>
<tr>
<td>Inadequate pain relief and/or intolerable side effects from</td>
</tr>
<tr>
<td>systemic agents</td>
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<tr>
<td>Favorable response to screening trial</td>
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<tr>
<td>Nonmalignant pain</td>
</tr>
<tr>
<td>Objective evidence of pathology</td>
</tr>
<tr>
<td>Psychological clearance</td>
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<tr>
<td>Inadequate pain relief and/or intolerable side effects from</td>
</tr>
<tr>
<td>systemic agents</td>
</tr>
<tr>
<td>Lack of drug-seeking behavior</td>
</tr>
<tr>
<td>Favorable response to screening trial</td>
</tr>
</tbody>
</table>
Screening Trial Techniques

Although most clinicians recommend a screening trial prior to pump placement, a screening protocol that accurately predicts a successful outcome has not been established (Krames, 1993; Maniker et al, 1991; Waldman et al, 1986; Paice et al, 1996). In general, screening trials can be divided into the following: 1) single injection, 2) multiple injections, 3) continuous infusion. There are no studies supporting one over the other and the clinician should use their own judgment to decide which technique best suits their practice. It is recommended that the initial screening be done as an inpatient in a monitored setting. After 24 hours of observation, the patient may have the drug continuously infused in the comfort of their home.

The single injection technique involves a single administration of drug intrathecally or epidurally. The morphine dose is usually 0.5-1.0mg intrathecally or 5-10 mg epidurally. An intrathecal or epidural equivalent of the patients daily systemic dose may also be used (see table 4). It has the advantages of low cost, low risks and ease of the technique. Disadvantages are lack of correlation with a continuous infusion and more likely to have a placebo response.

With the multiple injection technique, the patient is administered a series of injections, either intrathecally or epidurally. Morphine doses are similar for the single injection technique. Advantages of this technique are that the patients may receive a placebo injection for comparison with actual drug administration. A disadvantages is lack of correlation with a continuous infusion.

A continuous infusion may be administered intrathecally or epidurally through a temporary catheter connected to an external pump (Bedder 1990, Penn and Paice, 1987). The response to therapy can be determined over days to weeks. The initial morphine dose is 20 μg/hour intrathecally or 200 μg/hour epidurally or the equivalent to the patients daily systemic dose. The dose may be increased every 12-48 hours until pain relief or unacceptable side effects are reached. The advantage of this method is that it more closely mimics the implantable system. In addition, response to therapy can be more accurately assessed in the patients own environment performing their normal daily activities. The single injection and multiple injections are performed in the clinic or hospital setting making it difficult to accurately assess the patient’s response.

Assessments that should be made to determine the success of the trial are similar for all three techniques and should include an assessment of the following; 1) pain, 2) function, 3) mood, 4) side effects. There are no studies providing guidelines on the level of improvement in these assessments that is required to predict long-term success. Therefore, it is left to the judgment of individual practitioners to determine what they feel is a successful trial.

Patients with malignant pain should not be withdrawn from their systemic opioids. The trial should be initiated and systemic opioids tapered over 1-2 weeks as the intraspinal dose is increased. Non-malignant pain patients may or may not be withdrawn from systemic opioids prior to the screening trial. Even with the intraspinal delivery of opioids, systemic opioids should be tapered slowly over 1-2 weeks to avoid withdrawal.

If the patient fails a morphine trial, other agents may be used as discussed in the pharmacology section above. The choice of these agents will be based on the judgment of the practicing physician as no studies support one over the other. Since morphine is the only FDA approved agent for intrathecal analgesia, it is reasonable to start with this agent and proceed to other agent only after failure.
Psychological Screening

Most experts will agree that psychological screening is mandatory prior to embarking on chronic intraspinal drug therapy. In spite of this consensus, there are few reports on the efficacy of psychological screening in predicting outcome. This probably reflects the research challenges in this area and the difficulties in predicting long-term success based on psychological screening. However, there are some reports in the literature supporting psychological screening and in general these studies find that patients with a psychological profile deemed appropriate for implantable therapy have better outcomes than those deemed inappropriate (Kupers et al, 1994). However, there are some early reports that question the utility of a psychological evaluation in predicting outcome. Several studies state that depression, hysteria, and hypochondriasis are so common in pain patients and do not constitute a contraindication to implants (Burton, 1975 and 1977; Shealy, 1975; Brandwin and Kewman, 1982). Burton went as far as to question the need for psychological evaluation per se, but did admit that psychological testing can identify significant problems that may interfere with long-term success. There have been others that have agreed with this belief (Simpson, 1994), however, specialists with the most experience with implantables for pain relief hold strong to the belief that psychological screening is crucial to the long-term success of implantables for chronic pain management (North et al, 1991, 1993). Most of this literature involves spinal cord stimulation, however, this information can be applied to chronic intraspinal drug delivery.

Most of the studies in this area use the Minnesota Multiphasic Personality Inventory (MMPI) as a predictor of outcome with spinal implantables. North et al reported on the predictive value of psychological testing on the outcome of spinal cord stimulation (North et al, 1996). He concluded that low scores on two psychological traits, anxiety and problems with authority (as measured by the Derogatis Affects Balance Scale and the Wiggins scales of the MMPI, respectively) predicted pain relief following a spinal cord stimulation trial but not 3 months after permanent electrode implantation. However, they pointed out that their sample could have been biased but they still supported psychological screening. Burchiel et al studied 40 patient with chronic low back and leg pain who underwent spinal cord stimulation. They used the MMPI, the visual analogue pain rating scale (VAS), the McGill Pain Questionnaire (MPQ), the Oswestry Disability Questionnaire, the Beck Depression Inventory, and the Sickness Impact Profile to predict treatment outcome. Regression analysis revealed that increased patient age and MMPI D subscale scores correlated with poor outcomes. Higher scores on the evaluative subscale of the MPQ correlated with an improved outcome. From this study, they developed the following equation which correctly predicted success or failure at 3 months in 88% of their patients: % delta VAS = 112.57 – 1.98 (D) – 1.68 (Age) + 35.54 (MPQe).

Brandwin and Kewman found that treatment-resistant patients had relatively lower hysteria and hypochondriasis scores than the successful patients. They also concluded that higher elevations of the depression scale was associated with treatment failure. Daniel et al used a 6 point rating scale based on the results of a psychological interview, a pain questionnaire, a health index, the Cornell Medical Index, the McGill Pain Questionnaire, the Beck Depression Inventory, and the MMPI (Daniel, 1985). They reported a 76.5% accuracy in the psychologists predicting outcome based on this scale.

In a focus article, Nelson et al summarized certain psychological-behavioral features that would exclude a patient from further consideration for implantable therapy (Nelson et al, 1996). These include the following:

Active psychosis. A psychotic patient can have very real pain but their perception of the pain is often distorted. If the psychotic patient is stabilized on neuroleptics, they may be reconsidered for implantation but carefully monitored.
Active suicidality  Stabilization of the suicidal thoughts and associated mood disturbances is necessary before further consideration.  
Active homicidality  It is quite difficult to stabilize these individuals and they are often too unstable to engage in any treatment of this sort.

Major uncontrolled depression or other mood disorders  Patients with severe depression may experience increases in pain.  If the depression is treated, there pain may decrease significantly to eliminate the need for invasive therapy.

Somatization disorder or other somatoform disorders  These patients are at risk of developing other symptoms in response to the implant.  This exclusionary criteria should be used with caution as many chronic pain patients have vague pain complaints with no identifiable etiology.  
Alcohol or drug dependency  Patients with major alcohol or drug problems who demonstrate a minimum of 3 months of appropriate control of substance use may be reconsidered.

Compensation or litigation resolution  Although treatment obstacles may occur if the patient has a monetary incentive to remain disabled by pain, most pain experts agree that these patients should be evaluated on a case-by-case basis for implantable therapy.

Lack of appropriate social support  This is not an absolute exclusionary criteria but should be considered as the pain treatment team cannot assume all responsibility for the patient’s needs.

Neurobehavioral cognitive deficits  Severe cognitive impairments may interfere with the patient’s reasoning and judgment making it difficult for them to assume the shared responsibility required for implantable therapy.

In summary, psychological testing serves as a screening tool to identify the appropriateness of invasive therapy for the management of chronic pain.  Using the exclusionary criteria of Nelson et al, the psychological evaluation should focus on identifying these problems that may interfere with a successful outcome.  As our medical judgment on the treatment of chronic pain is not infallible, neither is psychological screening.  However, when the two are used together, only positive results will follow.

ECONOMICS OF CHRONIC SPINAL DRUG DELIVERY FOR ANALGESIA

One of the most controversial topics in defining outcomes is “cost of therapy”.  The weight applied to this outcome varies upon who is doing the analysis: the patient, the provider, or the payor.  From a payors perspective, the bottom line is cost and they tend to place less emphasis on quality of life and pain relief.  From a patient’s perspective, the bottom line is pain relief and from a providers perspective the bottom line is fewer emergency room visits and fewer phone calls.  Therefore, the economics of therapy is a very difficult assessment and it is yet to be determined if there are true cost savings with long-term intraspinal drug therapy.

The most comprehensive assessment of this issue was presented by de Lissovoy et al who looked at the cost-effectiveness of long-term intrathecal morphine for failed back syndrome (Lissovoy et al, 1997).  They used a cost-effectiveness analysis (Hassenbusch et al, 1997) to compared the direct costs of intrathecal pain therapy via an implanted pump to medical management alone for failed back surgery patients over a 5-year period.  Base-case, worst-case, and best-case scenarios were developed by a panel of experts.  They did not include charges for repeat back surgery into the analysis.  They concluded that the base-case costs for intrathecal drug therapy were less than medical management over at 22 months.
Other studies have compared the costs of different routes of delivery. Bedder et al.
compared the cost of the epidural morphine delivered via an external pump to intrathecal
delivery. They concluded that although the initial costs for an intrathecal pump implant are
higher (1.67 times higher), the break-even point appeared at 3 months and at 1 year the total
charges for the epidural group were approximately twice as high as the intrathecal group.
Another similar study compared different routes of delivery for opioids in the management of
cancer pain (Hassenbusch et al, 1997). The authors believe this model could be applied to
nonmalignant pain. Five different routes of administration were studied: oral, transdermal,
subcutaneous/intrathecal via an external infusion pump, epidural via an external infusion pump,
and intrathecal delivery via an implanted infusion pump. They used an empirical dose rate of
10mg/hour of intravenous morphine equivalent for the cost comparison. If the dose remains
constant, they concluded that at 25 months oral and transdermal delivery were the least
expensive followed by the intrathecal delivery with an implanted infusion pump followed by
the epidural and subcutaneous delivery via an external infusion pump. If one assumed a 5% per
month increase, they concluded that at 25 months intrathecal delivery was the least expensive
followed by the oral and transdermal delivery followed by the epidural and subcutaneous
delivery via an external infusion pump.

These studies demonstrate cost savings with intrathecal drug delivery using an implanted
infusion system over a few years. It is yet to be determined if there are cost savings over the life
of the patient but these studies suggest savings. However, only a portion of the picture is
captured with these studies and there may be far-reaching significance to the patient, payor,
provider and society as a whole.

REFERENCES

Klepper ID, Choi Y, Kimball S, Chu G (1987) Epidural butorphanol or morphine for the
relief of post Cesarean section pain: ventilatory responses to carbon dioxide, Anesth Analg
66: 887-893
2. Abram SE, O'Connor TC: Characteristics of the analgesic effects and drug interactions of
3. Abram SE, Winne RP: Intrathecal acetyl cholinesterase inhibitors produce analgesia that is
4. ADD references
5. Aguilar JL; Roca G; Montes A; Gonzalez-Carrasco FJ; Valles J; Vidal F. [Experience with
the Du Pen epidural catheter in chronic cancer pain]. Revista Espanola de Anestesiologia y
6. Aimone LD, Yaksh TL. Opioid modulation of capsaicin-evoked release of substance P
from rat spinal cord in vivo, Peptides 1989; 10: 1127-1131
7. Ali NMK. Hyperalgesic response in a patient receiving high concentrations of spinal
8. Aran, S., Proudfit, H.K., Antinociceptive interactions between intrathecally administered
alpha noradrenergic agonists and 5'-N-ethylcarboxamide adenosin. Brain Research, 519


30. Bowersox SS; Gadbois T; Singh T; Pettus M; Wang YX; Luther RR. Selective N-type neuronal voltage-sensitive calcium channel blocker, SNX-111, produces spinal antinociception in rat models of acute, persistent and neuropathic pain. Journal of Pharmacology and Experimental Therapeutics, 1996 Dec, 279(3):1243-9


34. Brose WG; Gutlove DP; Luther RR; Bowersox SS; McGuire D. Use of intrathecal SNX-111, a novel, N-type, voltage-sensitive, calcium channel blocker, in the management of intractable brachial plexus avulsion pain. Clinical Journal of Pain, 1997 Sep, 13(3):256-9


44. Castro-Lopes JM; Malcangio M; Pan BH; Bowery NG. Complex changes of GABA and GABAB receptor binding in the spinal cord dorsal horn following peripheral inflammation or neurectomy. Brain Research, 1995 May 15, 679(2):289-97.


56. Chrubasik J; Meynadier J; Blond S; Scherpereel P; Ackerman E; Weinstock M; Bonath K; Cramer H; Wunsch E. Somatostatin, a potent analgesic [letter]. Lancet, 2:1208-9, 1984


68. Damaj MI; Fei-Yin M; Dukat M; Glassco W; Glennon RA; Martin BR. Antinociceptive responses to nicotinic acetylcholine receptor ligands after systemic and intrathecal administration in mice. Journal of Pharmacology and Experimental Therapeutics, 1998 Mar, 284(3):1058-65.
71. De Cicco M; Matovic M; Castellani GT; Basaglia G; Santini G; Del Pup C; Fantin D; Testa V. Time-dependent efficacy of bacterial filters and infection risk in long-term epidural catheterization. Anesthesiology 82:765-71, 1995.
75. Delfs JR; Dichter MA. Effects of somatostatin on mammalian cortical neurons in culture: physiological actions and unusual dose response characteristics. Journal of Neuroscience, 3:1176-88, 1983
95. Feldman JM; Chapin-Robertson K; Turner J. Do agents used for epidural analgesia have antimicrobial properties? Regional Anesthesia 19:43-7, 1994.


129. Kakinohana O, Taira Y, Kakinohana M, Okuda Y, Yaksh TL. Spinal 2-choroadenosine administration inhibits thermal hyperalgesia and concurrent glutamate release evoked by intrathecal NMDA infusion. Anesthesiology 89: A1130

130. Kaneko S; Fukuda K; Yada N; Akaike A; Mori Y; Satoh M. Ca2+ channel inhibition by kappa opioid receptors expressed in Xenopus oocytes. Neoreport, 5(18):2506-8, 1994.


144. Kristensen JD; Karlsten R; Gordh T; Berge OG. The NMDA antagonist 3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP) has antinociceptive effect after intrathecal injection in the rat. Pain, 1994; 56:59-67.


146. Lakhiani PP; MacMillan LB; Guo TZ; McCool BA; Lovinger DM; Maze M; Limbird LE. Substitution of a mutant alpha2a-adrenergic receptor via "hit and run" gene targeting reveals the role of this subtype in sedative, analgesic, and anesthetic-sparing responses in vivo. Proceedings of the National Academy of Sciences of the United States of America, 1997 Sep 2, 94(18):9950-5.


163. Malmberg AB, Yaksh TL. Voltage-sensitive calcium channels in spinal nociceptive processing: Blockade of N-


173. Marx S: Medullary narcosis during labor. Med Record 58: 521-527, 1900

174. Matas R: Local and regional anesthesia with cocaine and other analgesic drugs, including the subarachnoid method, as applied in general surgical practice. Philadelphia Med J 6: 820-843, 1900


179. Meynadier J; Chrubasik J; Dubar M; Wunsch E. Intrathecal somatostatin in terminally ill patients. A report of two cases. Pain, 23:9-12, 1985

514
185. Mollenholt P; Post C; Paulsson I; Rawal N. Intrathecal and epidural somatostatin in rats: can antinociception, motor effects and neurotoxicity be separated? Pain, 43:363-70, 1990.
186. Mollenholt P; Rawal N; Gordh T Jr; Olsson Y. Intrathecal and epidural somatostatin for patients with cancer. Analgesic effects and postmortem neuropathologic investigations of spinal cord and nerve roots Anesthesiology, 199, 81:534-42.


204. Ono N; Kroin JS; Penn RD; Paice JA. Effects of intrathecal nonnarcotic analgesics on chronic tactile allodynia in rats: alpha 2-agonists versus somatostatin analog. Neurologia Medico-Chirurgica, 1997 Jan, 37(1):6-10;


216. Patel YC; Greenwood MT; Warszynska A; Panetta R; Srikanth CB. All five cloned human somatostatin receptors (hSSTR1-5) are functionally coupled to adenylyl cyclase.
227. Piros ET; Prather PL; Loh HH; Law PY; Evans CJ; Hales TG. Ca2+ channel and adenylyl cyclase modulation by cloned mu-opioid receptors in GH3 cells. Molecular Pharmacology, 47(5):1041-9, 1995.
235. Raynor K; Murphy WA; Coy DH; Taylor JE; Moreau JP; Yasuda K; Bell GL; Reisine T. Cloned somatostatin receptors: identification of subtype-selective peptides and demonstration of high affinity binding of linear peptides. Molecular Pharmacology, 1993 Jun, 43(6):838-44.


239. Reisine T; Kong H; Raynor K; Yano H; Takeda J; Yasuda K; Bell GI. Splice variant of the somatostatin receptor 2 subtype, somatostatin receptor 2B, couples to adenylyl cyclase. Molecular Pharmacology, 44:1016-20, 1993.


251. Sato K; Kiyama H; Park HT; Tohyama M. AMPA, KA and NMDA receptors are expressed in the rat DRG neurones. Neuroreport, 1993 Sep 10, 4(11):1263-5.


274. Smith GD; Harrison SM; Wiseman J; Elliott PJ; Birch PJ. Pre-emptive administration of clonidine prevents development of hyperalgesia to mechanical stimuli in a model of mononeuropathy in the rat. Brain Research, 1993; 632:16-20.
279. Stanfa LC; Dickenson AH. Electrophysiological studies on the spinal roles of endogenous opioids in carrageenan inflammation. Pain, 1994; 56:185-91
280. Stanfa LC; Sullivan AF; Dickenson AH. Alterations in neuronal excitability and the potency of spinal mu, delta and kappa opioids after carrageenan-induced inflammation. Pain, 1992; 50:345-54
286. Sucher NJ; Awobuluyi M; Choi YB; Lipton SA. NMDA receptors: from genes to channels. Trends in Pharmacological Sciences, 17:348-55, 1996.
289. Tait D and Caglieri G: Experimental and clinical notes on the subarachnoid space. JAMA 35: 6-10, 1900
293. Tata AM; Biagioni S; Ricci A; Amenta F; Augusti-Tocco G. Muscarinic cholinergic receptors in dorsal root ganglia of chick embryo: a radioligand binding and immunocytochemical study. Neuroscience Letters, 1995 Apr 21, 189(3):139-42.
294. Tiseo PJ; Yaksh TL. Dose-dependent antagonism of spinal opioid receptor agonists by naloxone.


335. Yamamoto T, and Yaksh TL. Comparison of the antinociceptive effects of pre- and post-treatment with intrathecal morphine and MK801, an NMDA antagonist, on the formalin test in the rat. Anesthesiology 77: 757-763, 1992a.


Topical and Oral Anesthetics in Cancer Pain Management

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INTRODUCTION

The clinical use of the sodium channel blockers (SSCB) date back to the 1940s where reports emerged describing the analgesic effects of the systemically administered sodium channel blockers (SSCB) in acute pain [1-3]. Soon thereafter, it was recognized that SSCBs were also effective in treating chronic painful conditions [3-5]. These initial reports led to an abundance of preclinical and clinical studies supporting the use of topical and systemic sodium channel blockers for the treatment of chronic pain.

Peripheral nerve injury and inflammation lead to a spontaneous and evoked pain that is thought to be in part mediated by voltage sensitive sodium channels. The spontaneous pain occurs at the level of the injured axons and in the dorsal root ganglion cells. Preclinical studies have demonstrated that this spontaneous and evoked pain can be decreased with the delivery of SCBs. In addition, clinical studies are supporting the topical application of sodium channel blockers for the treatment of a variety of pain syndromes.

This chapter will discuss the use of the topical and systemically delivered SCBs for the treatment of pain. First the neurophysiology of the sodium channel as it relates to pain transmission will be discussed. Second, the clinical literature will be reviewed on the use and efficacy of topical and systemically delivered SCBs in the treatment of pain.

SODIUM CHANNEL BLOCKERS AND NOCICEPTION

Several lines of evidence suggest that both the spontaneous and evoked pain after nervous system injury is mediated in part by an increase in the density of voltage-sensitive sodium channels in the injured areas of the axon and dorsal root ganglion of the injured axon [6-8]. In animal models of neuropathic pain, it has been demonstrated that spontaneous and evoked pain is significantly diminished after delivery of sodium channel antagonists [9-12]. Importantly, these effects occur at plasma concentrations that do not produce an afferent conduction block [13].

The development of the spontaneous and evoked pain after nervous system injury is thought to be due not only to a change in number of sodium channels but also a change in the distribution, and type of sodium channels. These changes occur at the area of injury, demyelination and dorsal root ganglion. These sodium channels display marked pharmacological differences from the uninjured state. For example, it is speculated that in the presence of injury, sodium channels on C fibers display a significant increase in affinity and an exaggerated response to sodium channel blockade as opposed to the uninjured state [14]. Therefore, it has been suggested that neuropathic pain is more responsive to SSCBs than nociceptive pain. Indeed it has been demonstrated that the SSCBs have no effect on acute nociceptive processing whereas there is a significant effect on pain after tissue injury and nerve injury. At plasma lidocaine concentrations of up to 3 μg/ml, there are no prominent effects on acute heat, cold, or mechanical thresholds [15, 16]. A similar lack of effect on acute nociceptive processing has been demonstrated with mexiletine, an oral bioavailable analog of lidocaine, at plasma concentrations of up to 0.5 μg/ml [17]. Two other studies have demonstrated a significant effect of intravenous lidocaine on acute ischemic pain (a model of acute nociceptive processing) [18, 19]. However, the plasma concentrations were above 3 μg/ml plasma level which typically exceed the maximal tolerable dose. In contrast, IV lidocaine has been demonstrated to significantly reduce postoperative pain with achieved plasma levels of 1-2 μg/ml [20, 21]. In addition, there are numerous reports on the efficacy of the SSCBs in neuropathic pain disorders (see discussion below).
Sodium channels are present throughout the body including nerves, muscle and heart. At least seven different sodium channels have been isolated all with important biophysical and pharmacologic differences resulting in differing sensitivities to sodium channel blockers. Sodium channels are classified by their sensitivity to tetrodotoxin (TTX), a potent sodium channel blocker. TTX sensitive (TTXs) sodium channels are blocked by small concentrations of TTX whereas TTX-resistant (TTXr) sodium channels are not blocked even when exposed to high concentrations of TTX. The role of TTXs and TTXr sodium channels in nociception is controversial; however, as described above it is clear that after nerve injury and during inflammation, there are dynamic and expression changes that occur in both TTXs and TTXr sodium channels. [22]

Proponents for the TTXr sodium channel as being important in nociception argue that because of their different voltage sensitivities of activation and inactivation, TTXr channels are still capable of generating impulses at depolarized potentials (which characterize the chronically damaged nerve fibers), whereas TTXs channels are inactivated and cannot contribute to excitability. For example, PN3 is a subclass of the TTXr sodium channel that is located only in the peripheral nervous system on small neurons in the dorsal root ganglion and is thought to be specific to pain transmission [23]. Animal models of experimental nerve damage have demonstrated changes in expression and distribution of the PN3 sodium channel; therefore, SSCBs specific to the PN3 sodium channel could have important clinical implications [24, 25]. Indeed, Faravelli and coworkers have demonstrated a marked hyperalgesic effect of a selective TTXr sodium channel blocker in animal models.

It has been demonstrated in animal models of spinal nerve ligation that application of TTX of approximately two orders of magnitude lower than those needed to block TTXr sodium channels resulted in a significant reduction of ectopic discharges in the dorsal root ganglion cells. This suggests that the TTXs subtype of sodium channels may be important in generating neuropathic pain [26, 27]. Therefore, it is unclear as to what type, if any, of the sodium channels are important to the development of nociceptive pain.

Inflammation is also thought to lead to changes in sodium channel expression. In the presence of inflammation, sodium channel plasticity is thought to result from increase in nerve growth factor (NGF). Whereas axotomy reduces the amount of NGF in the DRG, inflammation increases the amount of NGF in the DRG [28]. Patterns of sodium channel expression can be quite different between inflammation and nervous system injury; however, both tend to increase DRG excitability through these changes. In inflammatory conditions, such as osteoarthritis, animal studies have reported clinically active abnormal sodium channels, which when antagonized, reduce spontaneous nociceptive activity and alleviate pain behaviors of the rodent [10,11]. Lidocaine, a topically and systemically administered sodium channel blocker, has also been shown to inhibit the expression of nitric oxide and subsequent release of pro-inflammatory cytokines from T-cells and, thus, provides another potential analgesic mechanism for the lidocaine patch in the treatment of inflammatory pain conditions. [12]

CLINICAL USE OF THE SODIUM CHANNEL BLOCKERS AND PAIN

Topical Agents

Peripheral mechanisms of pain are inherent in most pain states including acute and chronic pain, and neuropathic, inflammatory, and cancer pain. These peripheral mechanisms are believed to be clinically relevant sources of pain and, thus, appropriate targets for drug therapy[29]. Topical treatment by definition provides clinically meaningful levels of drug
delivered directly to the peripheral tissues, including nerve and soft tissue, via a patch or poultice, without any relevant systemic activity.

While there are many treatment options and combinations for pain, including cancer pain, the choice of treatment relies on three important criteria: 1) efficacy—demonstrated in controlled clinical trials; 2) safety—demonstrated in controlled clinical trials and subsequent clinical experience; 3) favorable tolerability profiles (ie, side effects, drug/drug interactions). The efficacy of treatment does not necessarily match its invasiveness and with increase invasiveness comes increase risks and costs. Due to the low risk and side effects associated with topical treatment, this mode of treatment is very attractive and should be considered early on in the pain treatment continuum when indicated. For some patients, topical medication can be at least as effective as systemic and more invasive therapies [30, 31]. Two topical sodium channel blockers are currently available in the United States—the lidocaine patch 5% (Lidoderm®, Endo Pharmaceuticals Inc., Chadds Ford, Penn), and eutectic mixture of lidocaine 2.5% and prilocaine 2.5% (EMLA®, AstraZeneca Pharmaceuticals LP, Wilmington, Del).

**Lidocaine Patch**
The lidocaine patch is a 10x14-cm topical patch comprised of an adhesive material containing 5% lidocaine (700 mg) in an aqueous base, which is applied to a nonwoven polyester felt backing and covered with a polyethylene terephthalate film-release liner. The release liner is removed prior to application. In addition to its sodium-channel–blocking activity, it has been suggested that the lidocaine patch acts as a protective barrier against cutaneous stimuli for patients with allodynia [29, 32]. The lidocaine patch delivers lidocaine directly to the painful area to produce an analgesic effect without loss of sensation. In addition, only a small amount (ie, 3% ± 2%) of lidocaine has been found to be absorbed in healthy subjects treated with the lidocaine patch; therefore it is unlikely that the pain relief from the lidocaine patch results from systemic absorption [30, 31, 33]. This is a major advantage over systemically administered sodium channel blockers where efficacy is often limited by side effects. The most common adverse reactions are local, in the skin region directly underlying the patch, and generally tend to be mild, resolving without the need for intervention [30, 31]. There have not been any serious systemic adverse events related to treatment with the lidocaine patch in 6 recent clinical trials to date [30, 31]. Of the 450 patients studied in these trials, the most frequently reported systemic adverse event was mild-to-moderate headache (1.8%). Other less common systemic adverse events included dizziness and somnolence (<1%).

The lidocaine patch is approved by the Food and Drug Administration for the treatment of post herpetic neuralgia (PHN). The current FDA-approved labeling recommends that patients apply up to 3 lidocaine patches to the most painful areas of intact skin and wear them for no more than 12 hours in a 24-hour period. Increasing the dosing to 4 lidocaine patches applied either once daily for 24 hours or twice daily every 12 hours for 3 consecutive days was shown to be safe and well tolerated in a pharmacokinetic study of 20 normal subjects. In this study, plasma lidocaine levels were approximately 14.3% of those associated with cardiac activity and 4% of those typically associated with toxicity [30]. A regimen of 4 lidocaine patches worn for 18 h/d for 3 consecutive days also was shown to be well tolerated in 20 normal subjects [31]. The lidocaine patch 5% should be used with caution in patients with severe hepatic disease and in those receiving antiarrhythmic or local anesthetic drugs. One to two weeks of therapy with the lidocaine patch may be required to determine whether a patient will experience satisfactory relief. However, 1 study reported that a very small subgroup of patients with PHN required up
to 4 weeks of treatment with the lidocaine patch to obtain maximal benefit [34]. No dose escalation is necessary and tolerance does not develop with the lidocaine patch [35, 36].

Although there are no specific studies on the efficacy of lidoderm patch in the treatment of cancer pain, there are numerous studies supporting the efficacy of the lidocaine patch in the treatment of numerous painful conditions, both nociceptive and neuropathic. Many of these studies include pain that can occur indirectly from cancer and cancer treatment (e.g. postherpetic neuralgia, peripheral neuropathy, low back pain, and osteoarthritis). In one study of refractory PHN, 24 of 35 patients reported slight or better pain relief (averaging scores at 4 and 6 hours), and 10 patients reported moderate or better relief [32]. An enriched enrollment study of 32 patients with PHN who were known responders to the lidocaine patch showed that the lidocaine patch provided significantly more pain relief than a vehicle patch, using “time to exit” as the primary endpoint [35]. In a prospective, randomized, controlled trial of 96 patients with PHN, the lidocaine patch was superior to a vehicle patch in reducing all common pain qualities associated with neuropathic pain (eg, “burning,” “dull,” “deep,” “superficial,” and “sharp” pains) [37]. Statistically significant reductions in pain interference with quality of life were noted with the lidocaine patch in a large (N = 332), open-label, effectiveness study [34].

In addition to studies in PHN, there is one study supporting the use of the lidocaine patch in the treatment of a variety of other peripheral neuropathic pain conditions. In a randomized placebo controlled cross-over study in 40 patients with peripheral neuropathic pain, it was demonstrated that lidocaine patch significantly reduced pain over the 7 day treatment period. Number needed to treat was 4.4 which is comparable to other studies (NNT=3.2 – 5.0)[38]. In an open-label trial, the lidocaine patch improved pain in patients with a variety of refractory neuropathic conditions with allodynia, including post-thoracotomy pain, stump neuroma pain, intercostal neuralgia, painful diabetic polyneuropathy, meralgia paresthetica, complex regional pain syndrome, radiculopathy, and postmastectomy pain: 13 of 16 patients reported moderate or better pain relief with the lidocaine patch [39].

A unique feature of the lidocaine patch 5% is that it provides analgesia without anesthesia. Even with Q24 hour dosing, both light touch and pinprick sensation have been shown to be preserved [30].

**Euteric Mixture of Local Anesthetics (EMLA)**

EMLA cream is a mixture of lidocaine 2.5% and prilocaine 2.5% which is available as an oil based cream. It is generally applied to intact skin under an occlusive dressing. EMLA is approved by the Food and Drug Administration as a topical agent for use on normal intact skin for local analgesia, on genital mucous membranes for superficial minor surgery, and as pretreatment for infiltration anesthesia.

Like the lidocaine patch, EMLA delivers the local anesthetic directly to site of application. However, unlike the lidocaine patch 5%, EMLA causes a time dependent sensory loss in the skin area (anesthesia) to which it is applied through sodium channel blocking activity. The onset of skin anesthesia depends primarily on the amount of cream applied. Skin anesthesia peaks 2-3 hours after application with an occlusive dressing and persists for 1-2 hours after removal. Disadvantages of EMLA as compared to lidocaine patch include poor patient compliance due to the inconvenience of using a cream, and production of a sensory loss which can be annoying. Like the lidocaine patch, there is limited absorption of the local anesthetics found in EMLA. The peak blood levels of lidocaine and prilocaine absorbed with the application of EMLA 60 g to 400 cm² are well below systemic toxicity levels. Thus, minimal systemic side effects or drug-drug interactions have been noted with EMLA. Like lidoderm patch the most common side
effect is a local reaction at the site of application in up to 56% of patients. These reactions are usually mild and transient, resolving spontaneously within 1-2 hours.

Although there are numerous studies supporting the use of EMLA cream for the approved indication of skin anesthesia prior to blood draws and surgical incisions, there are few studies evaluating the efficacy in the treatment of acute and chronic pain conditions. In one small study in PHN (N = 12), EMLA cream 5% applied for 24-hour periods significantly improved mean pain intensity 6 hours after application as measured by a visual analog scale [40]. In another small study in PHN (N = 11), 5% EMLA cream applied daily under an adhesive occlusive dressing for 5 h/d for 6 days had no significant effect on mean ongoing pain intensity as measured by a visual analog scale [41]. However, 8 patients reported that the number of painful attacks decreased by ≥50%. EMLA had significant benefit in a subset of 8 patients with tactile allodynia. In one double-blind, randomized study of women undergoing breast surgery for cancer (N = 45), EMLA cream 5% or placebo was applied 5 minutes prior to surgery and daily for 4 days during the postsurgical period. Acute pain at rest and with movement did not differ between the EMLA and control groups, and the analgesics consumed during the first 24 hours were the same. However, time to the first analgesia requirement was longer, and analgesic consumption during the second to fifth days was less in the EMLA group. Three months postoperatively, pain in the chest wall and axilla, and total incidence and intensity of chronic pain were significantly less in the EMLA versus the control group. The use of analgesics at home and abnormal sensations did not differ between the 2 groups [42].

Thus, while both lidocaine patch 5% and EMLA have local anesthetics as their active ingredients, they differ dramatically in their clinical use profile, most likely due to their very different formulations and penetrating-enhancing chemicals.

**Systemic Sodium Channel Blockers**

**Lidocaine**

Lidocaine has been the most widely studied in the treatment of a variety of pain states [43]. When examined in patients reporting significant pain secondary to a variety of pain states, subanesthetic doses of systemic lidocaine produce clinically relevant relief in diabetes[16, 44], nerve injury pain states[45, 46] [47], postherpetic neuralgia [48] central pain[49, 50], fibromyalgia [51], and migraine [52, 53]. The efficacy of intravenous lidocaine on postoperative pain, which represents a nociceptive pain mechanism, yields conflicting results. Two randomized placebo controlled trials using similar doses and achieving similar plasma lidocaine concentrations (1-2 µg/ml) showed conflicting results [20, 54]. One large open label study in 302 subjects suggested an analgesic effect of lidocaine in postoperative pain [21]. These studies suggest a differential effect of lidocaine on neuropathic pain versus nociceptive pain. After nerve injury, sodium channels seem to play a substantive role in pain processing. However, the role of the sodium channels in pain processing after inflammation is unclear (see discussion above). Although controversial, it is suggested that sodium channel blockade is less effective in nociceptive pain processing as opposed to neuropathic pain processing. Consistent with this theory, patients with peripheral nervous system injury report substantially more pain relief than those with pain of unknown etiology [55]. In addition, there appears to be a differential effect of intravenous lidocaine depending on the location of the nervous system injury. Galer et al reported substantially better pain relief after peripheral nervous system injury as opposed to central nervous system injury [55]. It has also been suggested that intravenous lidocaine may lead to a reduction in sympathetic activity with resulting pain relief in sympathetically mediated pain. While some reduction in sympathetic activity has been demonstrated after systemic lidocaine [56], this appears to be a minor consequence of lidocaine-evoked hypertension/
tachycardia with reflex sympathetic attenuation [14]. Consistent with this, a recent study by Wallace et al showed minimal effects of intravenous lidocaine on pain and allodynia of complex regional pain syndrome type I and II with plasma levels of up to 3 μg/ml plasma level [57].

Lidocaine can also be delivered intranasally and has been studied with conflicting results. In acute migrain, intranasal lidocaine was shown to significantly decrease the pain and rescue medication [58]. However, a report in myofascial facial pain failed to show a significant difference between intranasal lidocaine, cocaine, and placebo [59].

There are few studies on the effects of intravenous lidocaine on malignant pain. Three randomized controlled trials failed to show an effect of intravenous lidocaine on cancer bone pain [60], neuropathy secondary to cancer treatment [61] and malignant plexopathy [62]. Brose and Cousins reported on three cancer patients with cancer related neuropathic pain who responded to a continuous subcutaneous infusion of lidocaine. Plasma lidocaine levels were in the range of 2-5 μg/ml [63]. Kronenberg et al reported on eighty-three hospice patients who received intravenous lidocaine 2mg/kg over 20 minutes followed by 1-3 mg/kg/hour infusion for opioid refractory cancer pain. 58% experienced a major response (complete or nearly complete relief of pain); 24% had partial relief; and 18% experience no benefit (Kronenberg et al, submitted for publication). Although systemic lidocaine clearly is advantageous in peripheral neuropathic pain, the role in central neuropathic pain, nociceptive pain and cancer pain is unclear and further studies are needed.

Lidocaine can be administered intravenously or subcutaneously. It is available in concentrations ranging from 5-200mg/ml. The high concentration should be reserved for subcutaneous administration. The standard loading dose for pain is 2 mg/kg over 20-30 minutes followed by a continuous infusion of 1-3 mg/kg/hour. If monitoring plasma levels, the targeted concentration is in the range of 1-3 μg/ml which is well below the cardiac and nervous system toxicity level.

**Procaine**

Procaine was one of the first local anesthetics to be used systemically for the treatment of pain. An advantage of procaine is the extremely low toxicity when administered systemically. A disadvantage is the extremely short half life due to ester hydrolysis by plasma pseudocholinesterases and red cell esterases [64]. The earliest use of procaine was to supplement general anesthesia and to treat chronic musculoskeletal disorders [3, 65]. It has also been shown anecdotally to be effective in the treatment of postherpetic neuralgia [4, 5]. There is one controlled study using procaine 4-6.5 mg/kg which show efficacy in postoperative pain [66]. There are no studies using procaine for the treatment of cancer pain.

**Mexiletine**

Mexiletine is an oral sodium channel antagonist that is structurally similar to lidocaine. Mexiletine has been reported to be effective in a variety of neuropathic pain syndromes including diabetic neuropathy [67, 68], alcoholic neuropathy [69, 70], peripheral nerve injury [71-73], and thalamic pain [74]. However, more recent reports question the efficacy of oral mexiletine in neuropathic pain [75-77].

There are two double-blind, placebo-controlled studies on mexiletine in neuropathic pain which showed an affect on spontaneous pain scores in diabetic neuropathy and peripheral nerve injury [68, 72]. However, there are four double-blind, placebo-controlled studies that show no significant effect of mexiletine on neuropathic pain scores in diabetic neuropathy, spinal cord dysesthetic pain and neuropathic pain with allodynia [67, 76-78]. In a double-blind, randomized placebo-controlled trial in diabetic neuropathy, Stracke et al showed a significant decrease in
specific components of neuropathic pain; however, they did not show any significant effect on pain scores using mexiletine doses up to 675 mg/day [67].

There are few studies in the literature correlating plasma levels of mexiletine with analgesia. Nishiyama and Sakuta concluded that the minimum effective plasma concentration for alcoholic neuropathy was 0.66 µg/ml [69]. Wallace et al showed that a peak level of 0.54 µg/ml plasma level did not result in pain relief if neuropathic pain [78]. The only other study that measured plasma concentrations was published by Galer et al. The mean highest tolerated dose was 878 mg (range 400 – 1200mg) with a mean serum level of 0.76 µg/ml. They found no correlation between mexiletine dose, serum level, and pain relief scores [45]. It is difficult to make firm conclusions on the predictive value of intravenous lidocaine on oral mexiletine success as claimed in the study by Galer et al because there are several reports in the literature on a prolonged pain relief from a single intravenous lidocaine infusion [16, 79, 80]. This may explain the lack of correlation between serum mexiletine level and pain relief in their study.

There are several reports in the literature on the dose-limiting side effects of oral mexiletine [45, 76]. These dose-limiting side effects often preclude achieving adequate therapeutic blood levels for pain relief. A study by Ando et al in healthy volunteers showed that the maximum tolerated plasma level was 0.5 µg/ml which is likely subtherapeutic [17]. Dose limiting side effects may account for the poor outcomes with this drug.

From studies evaluating the effective plasma level of mexiletine for the treatment of pain, it appears that the recommended daily dose is in the range of 1200-1500mg. However, as discussed above, this may be difficult to achieve due to dose-limiting side effects namely nausea. There are anecdotal reports of co-administering carafate to minimize the nausea thus allowing higher doses.

**Tocainide**

Tocainide is a derivative of lidocaine with anti-arrhythmic action which can be delivered orally. It has been demonstrated to have analgesic efficacy in a number of animal studies; however, there are few studies in humans [12, 81, 82]. In a double-blind crossover comparator study with carbamazepine in trigeminal neuralgia, tocainide was found to be equivalent to carbamazepine [83]. Carbamazepine is FDA approved for the treatment of trigeminal neuralgia.

**Flecainide**

The analgesic effects of flecainide was reported by Dunlop in 1988 [84]. Systemic flecainide has been demonstrated to suppress ectopic nerve discharge in neuropathic rats[85]. In spite of these reports, the clinical use of flecainide has been mixed. In an open label trial, Ichimata et al delivered intravenous flecainide to twenty patients with postherpetic neuralgia in which 15 responded. The responders received oral flecainide with chronic relief of the pain[86].

The use of flecainide in cancer pain has been ineffective. In a pilot study of 21 cancer patients with inadequately controlled pain with opioid analgesics, flecainide was of no benefit in 17 cases, two cases had clear-cut analgesic benefit and two cases had mild-moderate analgesic relief [75]. Bennett et al reported on a case of paranoid psychosis due to flecainide toxicity in malignant neuropathic pain and cautioned on use of flecainide in this vulnerable population[87].

**REFERENCES:**

Ziconotide: A Review

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Ziconotide (PRIALT®): a New Nonopioid Intrathecal Analgesic for the Treatment of Chronic Pain

Short running title: Ziconotide: a New IT Drug for Chronic Pain

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Summary

Ziconotide (PRIALT®) is a new nonopioid intrathecal (IT) agent recently approved for the treatment of chronic pain. Ziconotide is indicated for the management of severe chronic pain in patients for whom IT therapy is warranted and who are intolerant of or refractory to other treatment, such as systemic analgesics, adjunctive therapies, or IT morphine. Ziconotide blocks the N-type calcium channels located in the superficial dorsal horn of the spinal cord, resulting in potent analgesia. The efficacy of ziconotide has been demonstrated in three randomized placebo-controlled trials in over 500 patients. In addition, its safety has been demonstrated in over 1200 subjects. Ziconotide is a potent analgesic with a narrow therapeutic window. The drug requires a slow titration in order to achieve analgesia while avoiding dose-limiting side effects. This article reviews the currently available information on this new analgesic.

Keywords: Pain, Intrathecal, Calcium channel blocker, Ziconotide
INTRODUCTION

The prevalence of chronic pain has been estimated at 15% to 30% of the population in the United States alone [1]. Back pain is the most common chronic pain condition for which patients seek medical care and accounts for approximately $25 billion of health care expenditure annually [1-3]. The prevalence of neuropathic pain is estimated to be between 3 and 4 million cases per year in the United States, with neuropathic back pain being the most prevalent, followed by diabetic neuropathy and postherpetic neuralgia [4]. The high prevalence of pain underscores the need for better pain therapies for the treatment of chronic painful conditions.

The pain treatment continuum starts with the least invasive therapy and progresses to more invasive therapies. The efficacies of these treatments do not necessarily match their invasiveness, as noninvasive therapies, such as psychological counseling, physical therapies, and topical treatments, can be at least as effective as interventional techniques [5,6]. Patients suffering from chronic pain should start with noninvasive therapies, such as psychological therapies (meditation/relaxation), physical therapies, acupuncture, chiropractic, electrical stimulation, and topical treatments. If these treatments fail, the patient can progress to over-the-counter medications, such as the nonsteroidal anti-inflammatory agents, followed by nonopioid adjuvants, such as anticonvulsants and antidepressants. If the pain persists, the decision should be made to consider either nerve blocks or opioid therapy. Selection and management of patients on chronic opioids require an in-depth analysis of social environment, addictive potential, and compliance. If opioid therapy fails, the patient is then considered for more invasive therapies, such as spinal cord stimulation or intrathecal (IT) drug therapy. Selection of patients for implantable therapies requires detailed psychological and physical assessment, as well as a trial of either stimulation or drug infusion to determine responsiveness to therapy before implanting the device [7].

In 1981, the first IT pump using a constant flow rate pump system was implanted for the delivery of morphine in the treatment of chronic intractable pain [8]. Soon thereafter, the Medtronic pump was approved and became available for the delivery of baclofen in the treatment of spasticity. The US Food and Drug Administration (FDA) released this pump to the market in 1991, and it is now marketed as the commonly known SynchroMed® Infusion Pump (Medtronic Inc., Minneapolis, MN, USA). Until recently, morphine was the only drug FDA approved for the treatment of pain via the IT route. However, there are many drugs with a variety of mechanisms that are commonly delivered IT for the treatment of chronic pain, including opioids, sodium channel blockers, and alpha-2 agonists [9]. The following discussion will present a new IT agent that was recently approved and launched in the United States for the treatment of chronic pain and has a mechanism unique from that of other existing therapeutic options. The drug is approved and will be launched in parts of Europe this year.

INTRODUCTION TO THE COMPOUND

Ziconotide (PRIALT®, Elan Pharmaceuticals, Inc., San Diego, CA, USA) is the first new IT analgesic approved in the United States in more than 2 decades. It was approved on December 28, 2004, for use only in the Medtronic SynchroMed® EL, SynchroMed® II Infusion System and Smiths Medical MD, Inc., CADD-Micro® External Microinfusion Device and Catheter [10]. Ziconotide offers an effective nonopioid treatment option for severe chronic pain. It is a nonopioid analgesic that is the synthetic equivalent of a naturally occurring conopeptide found in the marine snail Conus magus.
Ziconotide is indicated for the management of severe chronic pain in patients for whom IT therapy is warranted and who are intolerant of or refractory to other treatment, such as systemic analgesics, adjunctive therapies, or IT morphine. Ziconotide can be considered for: 1) patients with severe chronic pain who are IT naïve and intolerant of or refractory to systemic analgesics and adjunctive therapies and 2) patients with severe chronic pain who are intolerant of or refractory to other IT therapies, such as IT morphine.

Ziconotide is formulated as a sterile, preservative-free, isotonic solution for IT administration. Ziconotide is available in either 1-, 2-, or 5-mL vials containing 100 mcg/mL of ziconotide, or a 20-mL vial containing 25 mcg/mL of ziconotide. Each vial is for single use only and is preservative free. The package insert outlines instructions for the use of ziconotide in the Medtronic SynchroMed® EL or SynchroMed® II Infusion System. The instructions are broken into three major categories: naïve pump priming, initial pump fill, and pump refills. For naïve pump priming (i.e., first-time use with ziconotide), only the undiluted 25-mcg/mL formulation should be used. The internal surfaces of the pump should be rinsed with 2 mL of ziconotide. This rinse should be repeated twice, for a total of three rinses. In a naïve pump, ziconotide is lost due to two factors that do not occur upon subsequent refills: 1) adsorption on internal device surfaces, such as the titanium, and 2) dilution in the residual space of the device. Consequently, the pump reservoir should be refilled with ziconotide within 14 days of the initial fill to ensure appropriate dose administration. The pump contents should be emptied prior to refill with ziconotide. For pump refills, ziconotide can be administered undiluted or diluted. The pump is filled at least every 40 days if diluted ziconotide is used. For undiluted ziconotide, the pump should be filled at least every 60 days. During transit and storage, ziconotide should be refrigerated. It should never be frozen and should be protected from light. Once diluted aseptically with preservative-free saline, ziconotide may be stored at 2°C to 8°C for 24 hours.

**PHARMACOLOGY**

Several lines of evidence developed in preclinical models suggest that both spontaneous and evoked pain are mediated in part by voltage-sensitive calcium channels [11]. Calcium channel blockers used in clinical practice are of the voltage-dependent type, in that the neurons must remain depolarized for a significant period of time for maximal blocking action to occur. This is in contrast to calcium channel modulators (i.e., pregabalin and gabapentin) that do not depend on neuron depolarization for effect. Calcium channel modulators decrease the amount of time the calcium channel remains in the open state, whereas calcium channel blockers block the calcium channel and prevent calcium entry. Both the central and peripheral nervous systems have an abundance of calcium channels.

There are six unique types of calcium channels expressed throughout the nervous system (designated L, N, P/Q, R, and T) [12,13]. L-type channels are located mainly on cell bodies and dendrites, and N-, P/Q-, and R-type channels are located at synaptic sites and are involved in neurotransmitter release, both excitatory and inhibitory [14-16]. The L-, N-, P/Q-, and R-type channels are high threshold, and the T-type is low threshold. Many studies have shown that L-, N-, P/Q-, and R-type channels are involved in nociception. The role of the T-type channel is unknown [17].

Ziconotide is the synthetic equivalent of a 25-amino acid, polybasic peptide found in the venom of the marine snail *Conus magus* [10]. Ziconotide binds to N-type calcium channels
located on the primary nociceptive (A-δ and C) afferent neurons in the superficial layers (Rexed laminae I and II) of the dorsal horn in the spinal cord [18,19] (Figure). Although the mechanism of action has not been established in humans, results in animals suggest that ziconotide binding blocks calcium entry into the presynaptic nerve terminal, thereby reducing the release of excitatory neurotransmitters from the primary afferent nerve terminals into the synapse [20]. There is one case report of spasticity due to spinal cord injury treated successfully with ziconotide [21]. This finding suggests that the site of action may also be on ventral horn synapses and perhaps interneurons.

The cerebrospinal fluid (CSF) volume of distribution for ziconotide (99.2 mL) after IT administration approximates the estimated total human CSF volume [22]. Median CSF clearance (CL) of ziconotide (0.26 mL/min) approximates the adult human CSF turnover rate, providing evidence that the primary mechanism for ziconotide CL is bulk CSF flow, rather than a metabolic process. The median elimination half-life of IT ziconotide from CSF in humans is 4.5 hours.

Intrathecal ziconotide is transported into the systemic circulation where part of it is bound to plasma proteins and degraded by proteolytic enzymes. Although formal pharmacokinetic (PK) drug-drug interaction studies have not been conducted with ziconotide, PK drug interactions are unlikely due to ziconotide’s low protein binding and low plasma concentrations following IT administration. Co-administration of ziconotide with other drugs that act on the central nervous system (CNS) may have an additive effect. There is no need for dose reduction in response to renal or hepatic failure.

Based on its elimination half-life (4.5 hours), ziconotide should reach steady-state levels in the spinal CSF in 24 hours. The discrepancy between the time to steady state concentration in the CSF and the time to onset of effects suggests that the distribution (penetration) of ziconotide into the spinal and brain tissues significantly lags the distribution into the CSF [22].
Efficacy

Ziconotide has been administered as a continuous IT infusion in 1254 patients in clinical trials, which represents 662 patient-years of treatment exposure [10]. The duration of treatment has ranged from a one-hour IT infusion to treatment lasting for more than 7.5 years. The mean duration of treatment was 193 days, with 173 patients (14%) treated for at least 1 year.

Two early randomized, placebo-controlled trials using IT ziconotide enrolled over 350 patients with severe, chronic, treatment-refractory, malignant [23] and nonmalignant [24] pain. The starting dose in these studies was 0.4 mcg/h (9.6 mcg/d), which was subsequently lowered to 0.1 mcg/h (2.4 mcg/d) due to unexpected intolerance. The dose was increased daily to a maximum dose of 2.4 mcg/h (57.6 mcg/d) in these hospitalized patients, according to a fixed, defined titration schedule, over 5 to 6 days until analgesia was obtained or intolerance developed. In both studies, the ziconotide-treated patients experienced a statistically and clinically significant reduction in pain compared to placebo-treated patients. Malignant pain patients treated with ziconotide reported a mean 53.1% improvement in Visual Analog Scale of Pain Intensity (VASPI) scores, compared to 18.1% improvement for patients receiving placebo (p<0.001) [23]; in the nonmalignant pain trial, mean improvement in VASPI scores was 31.2% among ziconotide-treated patients versus 6.0% in the placebo group (p<0.001) [24]. However, pain relief was accompanied by a high incidence of serious adverse events (SAEs) and frequent discontinuations due to adverse events (AEs).

A subsequent slow-titration study was conducted in which patients were randomized to receive ziconotide (n=112) or placebo (n=108) [25]. Ninety-seven percent of the subjects were determined by their physicians to be refractory to existing analgesic treatments. The IT infusion was started at 0.1 mcg/h (2.4 mcg/d), increasing gradually (0.05-0.1 mcg/h increments) over 3 weeks to a mean ziconotide dose of 0.29 mcg/h (6.96 mcg/d) at termination. Statistical significance was noted for mean percentage improvement in VASPI score from baseline to Week 3 (ziconotide [14.7%] versus placebo [7.2%], p=0.036) and for many of the secondary efficacy outcomes measures, such as the Clinical Global Impression measures of Satisfaction and Overall Pain Control. The slow titration of ziconotide to a low maximum dose was better tolerated than the faster titration to a higher mean dose used in two previous controlled trials. The dropout rate during titration for patients receiving ziconotide (8.0%) was similar to that for patients in the placebo group (7.4%) and far less than in the two fast-titration studies (32.4% and 28.4%); fewer AEs leading to discontinuation and SAEs were reported [25].

Although not FDA approved for the treatment of acute pain, ziconotide has been demonstrated to be effective in the treatment of acute postoperative pain. Thirty patients undergoing abdominal hysterectomy, radical prostatectomy, or total hip replacement surgery were randomized to receive placebo, a low dose (0.7 mcg/h) of IT ziconotide, or a high dose (7 mcg/h) of IT ziconotide [26]. There was a significant reduction in patient-controlled administration of morphine 24 to 48 hours postoperatively in patients receiving ziconotide. In addition, pain scores in the first 8 hours postoperatively were markedly lower in the ziconotide group. Four of 6 patients receiving the high dose reported significant side effects requiring the infusion to be discontinued in the first 24 hours.

Side Effects

The most frequently reported AEs (≥25% of patients) in the clinical trials (N=1254) were dizziness, nausea, confusion, headache, somnolence, nystagmus, asthenia, and pain [10]; AE
occurrence in the slow-titration study is summarized in Table 1. Compared with the fast-titration studies, the slow-titration study had a higher incidence of AEs related to higher cortical functions, such as memory impairment. Such differences could be attributable to the longer duration of the slow-titration study and the higher cumulative dose over 3 weeks, compared to only 5 to 6 days, in the two fast-titration studies.

Cognitive impairment may appear gradually after several weeks of treatment and appears to be dose dependent. The ziconotide dose should be reduced or discontinued if signs or symptoms of cognitive impairment develop, but other contributing causes should also be considered. The cognitive effects of ziconotide are generally reversible within 2 weeks after drug discontinuation. Even though ziconotide is essentially eliminated from the CSF after 24 hours, based on the elimination half-life discussed in the pharmacology section above, elimination from the brain parenchyma likely takes longer, thus explaining the delay in recovery from CNS side effects. Coadministration of ziconotide with other CNS-depressant drugs may increase the incidence of CNS side effects.

Patients have become unresponsive or stuporous while receiving ziconotide. The incidence of unresponsiveness or stupor in clinical trials was 2%. During these episodes, the patients’ breathing was not depressed, nor were there any cardiac effects. If reduced levels of consciousness occur, ziconotide should be discontinued until the event resolves; other etiologies, such as meningitis, should be considered. There is no known pharmacologic antagonist for this effect.

The US prescribing information for ziconotide contains a boxed warning for severe psychiatric symptoms and neurologic impairment. Severe psychiatric symptoms and neurological impairment may occur during treatment with ziconotide. Events of acute psychiatric disturbances, such as hallucinations (12%), paranoid reactions (3%), hostility (2%), delirium (2%), and psychoses (1%), have been reported in patients treated with ziconotide. Therefore, patients with a history of psychosis should not be treated with ziconotide. All patients should be monitored frequently for evidence of cognitive impairment, hallucinations, or changes in mood or consciousness. Ziconotide therapy can be interrupted or discontinued abruptly without evidence of withdrawal effects in the event of serious neurological or psychiatric signs or symptoms.

Ziconotide may cause or worsen depression with the risk of suicide in susceptible patients. In placebo-controlled trials, there was a higher incidence of suicide, suicide attempts, and suicidal ideation in ziconotide-treated patients (n=3) than in the placebo group (n=1) [10]. The incidence was 0.27 per patient-year for ziconotide patients and 0.10 per patient-year for placebo patients. Because there is a very large difference between the ziconotide group and the placebo group with respect to length of follow-up (662 patient-years versus 5.0 patient-years), it is very difficult to directly compare ziconotide and placebo suicide rates.

In the 1254 ziconotide-treated patients in clinical trials with an exposure of 662 patient-years, meningitis had an overall incidence of 3.2% (40 cases) in the ziconotide group, using either internal or external microinfusion devices, and 1% (one case) in the placebo group, which had an exposure of only 5 patient-years [10]. Because of the differences in patient-year exposure between the placebo and ziconotide group, it is difficult to draw conclusions on the risk of
meningitis. However, the incidence of meningitis seen in the patients receiving ziconotide does not appear to differ from that observed in the general population [27].

Forty percent of patients in ziconotide studies had serum creatine kinase (CK) levels above the upper limit of normal, and 11% had CK levels that were at least 3-fold greater than the upper limit of normal [10]. Most patients who experienced elevations in CK, even for prolonged periods of time, did not have limiting side effects. One case of symptomatic myopathy with electromyography findings and two cases of acute renal failure associated with rhabdomyolysis and extreme CK elevations have been reported. Therefore, it is recommended that physicians monitor serum CK periodically (every other week for the first month and monthly as appropriate thereafter) in patients undergoing treatment with ziconotide. In the event of the development of new neuromuscular symptoms (e.g., myalgias, myasthenia, muscle cramps, or asthenia), clinical evaluation, including the measurement of CK, should be performed. Should these symptoms continue and CK levels remain elevated or continue to rise, it is recommended that the physician consider ziconotide dose reduction or discontinuation.

No carcinogenicity studies have been conducted with ziconotide. Ziconotide did not affect male fertility in rats administered intravenous (IV) doses of up to 10 mg/kg per day for approximately 8 weeks (6500 times the maximum recommended human IT dose). Female fertility was significantly affected following IV administration at a dose of 10 mg/kg per day. Ziconotide was not teratogenic in rats with continuous IV infusion at doses of 30 mg/kg per day during the major period of organ development and has been classified as a pregnancy category C drug.

CONCLUSION, EXPERT OPINION, AND FIVE-YEAR VIEW

Ziconotide is a new nonopioid IT agent for the treatment of chronic pain. It is the first IT drug that has been subjected to rigorous double-blind, multicenter, placebo-controlled trials. These trials have demonstrated the drug’s efficacy in a treatment-refractory population. Ziconotide’s efficacy may be limited by side effects; however, clinical trials and experience suggest that a slow titration will minimize side effects and improve efficacy. Ziconotide is indicated for patients with severe chronic pain for whom IT therapy is warranted and who are 1) IT-naïve and refractory to less invasive treatments, such as systemic analgesics and adjunctive therapies, or 2) refractory to other IT therapies. The place of ziconotide in the continuum of IT therapies has yet to be determined since comparison trials with other IT agents have not been performed. In addition, the cost/benefit ratio of this new agent is unknown and should be considered when using ziconotide.

Ziconotide acts at a specific ion channel, the N-type calcium channel, and modulates one of the many pain mechanisms. Multiple pain mechanisms can co-exist in any given patient; therefore, current opinion considers treatments directed at different mechanisms likely to be more successful than treatments targeting a single mechanism. There is much interest in drug combination therapy, which includes ziconotide; however, combination trials with ziconotide have not been completed. Ziconotide is the first of what likely will be many IT agents for the treatment of chronic pain. The successful trials conducted with ziconotide are a milestone for IT therapy and will set the stage for future IT drug development.

Conflict of Interest

Dr. Wallace is a paid consultant and on the speakers bureau of Elan Pharmaceuticals, Inc.
REFERENCES
Papers of special note have been highlighted as:
* of interest
** of considerable interest
* Study demonstrates the importance of spinal cord calcium channels in pain transmission
**The first published paper demonstrating the efficacy of ziconotide in refractory pain**
Table 1. Adverse Events Occurring in ≥10% of Patients During Slow Titration [25]

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Patients, n (%)</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Ziconotide, n=112</td>
<td>Placebo, n=108</td>
<td></td>
</tr>
<tr>
<td>Any adverse event*</td>
<td>104 (92.9)</td>
<td>89 (82.4)</td>
<td></td>
</tr>
<tr>
<td>Dizziness*</td>
<td>53 (47.3)</td>
<td>14 (13.0)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>46 (41.1)</td>
<td>33 (30.6)</td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>25 (22.3)</td>
<td>13 (12.0)</td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>25 (22.3)</td>
<td>16 (14.8)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>21 (18.8)</td>
<td>18 (16.7)</td>
<td></td>
</tr>
<tr>
<td>Confusion*</td>
<td>20 (17.9)</td>
<td>5 (4.6)</td>
<td></td>
</tr>
<tr>
<td>Ataxia</td>
<td>18 (16.1)</td>
<td>2 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>17 (15.2)</td>
<td>13 (12.0)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>17 (15.2)</td>
<td>14 (13.0)</td>
<td></td>
</tr>
<tr>
<td>Abnormal gait*</td>
<td>17 (15.2)</td>
<td>2 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Memory impairment*</td>
<td>13 (11.6)</td>
<td>1 (0.9)</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>12 (10.7)</td>
<td>8 (7.4)</td>
<td></td>
</tr>
<tr>
<td>CK increased</td>
<td>12 (10.7)</td>
<td>4 (3.7)</td>
<td></td>
</tr>
<tr>
<td>Pruritis</td>
<td>9 (8.0)</td>
<td>11 (10.2)</td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>7 (6.3)</td>
<td>13 (12.0)</td>
<td></td>
</tr>
</tbody>
</table>

CK indicates creatine kinase.
*Significantly higher frequency among ziconotide-treated patients than in the placebo group (p≤0.05, Fisher exact test).
Figure legend

Ziconotide mechanism of action (courtesy of Elan Pharmaceuticals, Inc.).

Figure