

## CHAPTER 7

# MANAGEMENT OF POORLY RESPONSIVE PAIN

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Most patients attain a favorable balance between analgesia and side effects with gradual escalation of the opioid dose. However, some do not. The balance between analgesia and side effects varies from patient to patient given the same opioid and from opioid to opioid within the same individual. Some patients achieve analgesia that is maintained with few dosage adjustments; others are completely unresponsive and experience no pain relief at doses associated with intractable adverse effects. *Opioid responsiveness* refers to the probability that satisfactory relief without intolerable and unmanageable side effects can be attained during gradual dose titration.

Although some patients respond so poorly to multiple opioid trials that the term *opioid resistant* can be applied, the variability observed in responsiveness is such that this term should be avoided. No factor or group of factors is so predictive that either a negative or positive outcome can be known in advance of a therapeutic trial. Likewise, within-patient responsiveness to different opioids varies considerably, and a poor response to one opioid should not be interpreted as a poor response to opioid therapy overall.

### **Factors that influence opioid responsiveness**

Several factors influence responsiveness to opioids. Recognition of these factors may help in the development of strategies to improve the outcome of therapy.

#### ***Individual characteristics***

Demographic and disease-related factors may predispose to side effects, thereby reducing therapeutic responsiveness. For example, older patients may be less likely to experience a favorable outcome during opioid therapy because of a propensity to experience cognitive impairment from centrally acting agents. Comorbidities, such as brain metastases in cancer patients or dementia, may have the same effects.

#### ***Neuropathic pain***

Although several controlled trials have now shown that patients with certain types of neuropathic pain, such as painful diabetic polyneuropathy, can respond well to opioid analgesics, there is

some evidence that, overall, patients with neuropathic pain may be relatively less responsive than patients with nociceptive pain. Opioid therapy should not be withheld merely on the assumption that its mechanism precludes a favorable response, but the clinician should be prepared with alternative therapeutic strategies to use if needed.

### ***Breakthrough (incident) pain***

Breakthrough pains are transitory episodes that occur in the setting of an otherwise controlled or stabilized painful condition. The term *incident pain* is most commonly applied to breakthrough pains that occur as a result of a voluntary action (ie, effort-dependent pains). Opioid responsiveness may be impaired in patients with frequent and severe breakthrough pains, particularly when the onset is rapid and the duration is too short to allow effective use of supplemental doses of an oral opioid drug. For example, a patient with incident pain related to standing may not be able to achieve adequate control of pain with an oral opioid because severe pain flares that occur immediately with every effort to stand cannot be addressed in a timely way by the medication. In these cases, a trial of a rapidly acting “rescue” opioid (eg, oral transmucosal fentanyl, intravenous patient-controlled analgesia) or a completely different analgesic modality may be needed.

### ***Tolerance***

Opioid responsiveness would be impaired if analgesic effects declined rapidly, driving dose escalation ultimately to a level associated with intolerable side effects. The need for dose escalation to maintain effects is a complex phenomenon. It could be caused by analgesic tolerance or by any factor that induces more pain and, hence, the need for more analgesia.

If the requirement for dose escalation is driven by a factor that causes worsening pain, such as progression of a disease, then the phenomenon cannot be attributed to opioid tolerance alone. Surveys in the clinical setting have identified these alternative explanations as the norm. In the setting of nonprogressive disease, doses typically stabilize for prolonged periods. Concern about tolerance, therefore, should not inhibit opioid prescription to appropriate patients.

### ***Opioid metabolites and drug-drug interactions***

Morphine’s metabolites, morphine-3-glucuronide and morphine-6-glucuronide, are active and accumulate in the setting of renal insufficiency. Although the importance of these metabolites in determining opioid responsiveness is not yet clear, accumulation could be a

cause of poor morphine responsiveness in some patients. A similar situation presumably could occur with other opioids that have active metabolites and is widely recognized with those that have neurotoxic metabolites, notably meperidine and propoxyphene.

The potential for drug-drug interactions exists with some of the opioid analgesics, but little is yet known about the impact of these interactions on responsiveness. Codeine is metabolized to the active metabolite morphine by the CYP2D6 enzyme of the cytochrome P-450 hepatic enzyme system. Persons who are slow metabolizers at this isozyme site (about 7% of the US population) may have poor codeine responsiveness because of limited metabolism to morphine. It also is possible that drugs that compete at the CYP2D6 site, such as quinidine, may change the patient's drug responsiveness. Any drug that induces enzymatic activity at opioid metabolic (deactivation) sites could, in effect, reduce responsiveness.

### **Improving the balance between analgesia and side effects**

Patients with poorly responsive pain must be comprehensively assessed to identify the most rational therapeutic course. The selection of an approach is empirical; there are very few comparative trials, and every case suggests a variety of strategies that could be undertaken in an effort to improve pain control (table 19).

#### ***Opening the therapeutic window***

Management of side effects should be considered a routine part of opioid therapy. In the context of poor responsiveness, more aggressive management may be entertained in an effort to open the therapeutic window and potentially allow higher opioid doses (see chapter 6).

#### ***Opioid rotation***

Poor responsiveness during treatment with one opioid does not predict response to another. Sequential opioid trials—called opioid rotation—is now widely accepted for addressing poorly responsive pain (see chapter 5). When switching from one opioid to another, calculated equianalgesic doses (see chapter 3) are used as a starting point to reduce the risk of overdosing or underdosing (see table 12).

#### ***Pharmacologic techniques that reduce the systemic opioid requirement***

A reduction in the opioid dose necessary to yield therapeutic benefit may allow for a clinically relevant dose that is in the range

**Table 19. Alternative strategies for patients with poorly responsive pain**

Approach	Therapeutic options
Opening the therapeutic window	<ul style="list-style-type: none"> <li>• More aggressive treatment of side effects (eg, psychostimulant for sedation)</li> </ul>
Identifying an opioid with a more favorable balance between analgesia and side effects	<ul style="list-style-type: none"> <li>• Opioid rotation</li> </ul>
Using pharmacologic techniques to reduce systemic opioid requirement	<ul style="list-style-type: none"> <li>• Coadministration of nonopioid analgesic or adjuvant analgesic</li> <li>• Neuraxial drug infusion</li> </ul>
Using nonpharmacologic techniques to reduce systemic opioid requirement	<ul style="list-style-type: none"> <li>• Anesthesiologic approaches (eg, neural blockade)</li> <li>• Surgical approaches (eg, cordotomy)</li> <li>• Rehabilitative approaches (eg, brace, physical therapy)</li> <li>• Psychologic approaches (eg, cognitive therapy)</li> </ul>

not associated with treatment-limiting toxicity. Two pharmacologic strategies derive from this concept: systemic administration of a coanalgesic and delivery of the opioid intraspinally (neuraxial infusion).

**Systemic administration of coanalgesics.** Potential coanalgesics include the nonsteroidal anti-inflammatory drugs (NSAIDs) and the so-called adjuvant analgesics. NSAIDs (selective and nonselective agents) produce additive analgesia when combined with opioids, and the combination of an opioid and an NSAID has been included in widely accepted guidelines for treatment of both acute and cancer pain.

Adjuvant analgesic agents are drugs that have a primary indication other than pain relief but are known to have an analgesic effect in specific circumstances. They include numerous drugs in diverse drug classes. A simple taxonomy divides these classes by their current uses (table 20). The multipurpose drugs include a large number of analgesic antidepressants,  $\alpha_2$ -adrenergic agonists and corticosteroids and a variety of topical agents.

Drug classes used selectively for neuropathic pain include all the multipurpose analgesics plus the analgesic anticonvulsants,  $\gamma$ -aminobutyric acid agonists, oral local anesthetics, and *N*-methyl-D-aspartate receptor antagonists. Drugs that are indicated for musculoskeletal pains comprise the so-called muscle relaxants and benzodiazepines. Drug classes used for headache include the NSAIDs, the multipurpose agents and anticonvulsants,

and numerous classes specifically prescribed for vascular headache, including the vasoactive drugs,  $\beta$ -blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers.

Finally, there are some adjuvant analgesics used for certain types of cancer pain, specifically drugs for pain from bone metastases and those for pain associated with malignant bowel obstruction. Given the extraordinary variety of coanalgesics available, and the limited data on each, selection of specific drugs for trials in the patient with poorly responsive pain requires good clinical judgment informed by a comprehensive evaluation of the patient and a grounding in pharmacology.

**Neuraxial infusion.** The clearest indication for intraspinal opioid delivery is intolerable somnolence or confusion in patients who are not experiencing adequate analgesia and have pain located below the level of midchest. Intraspinal administration of local anesthetics or other agents (eg, clonidine) in combination with an opioid may provide additional analgesia and permit the successful treatment of patients whose pain is unresponsive to spinal morphine alone.

### ***Nonpharmacologic techniques that reduce the systemic opioid requirement***

Numerous nonpharmacologic approaches can be used to reduce the systemic opioid requirement (table 21). Like the pharmacologic strategies, selection of one or more of these approaches must be informed by an understanding of the available options and a detailed assessment of the patient.

**Anesthesiologic approaches.** Invasive therapies performed with a needle may be under the purview of a variety of medical disciplines. The more challenging and potentially risky of these approaches historically have been performed by anesthesiologists, whose training includes becoming skilled at regional anesthetic techniques. Injection therapies include trigger point injections, joint injections, and spinal injections of varied types. Neural blockade subsumes a broad array of procedures that target somatic or sympathetic nerves. Use of implanted analgesic devices, including spinal cord stimulators and neuraxial infusion pumps, is often considered under this category as well.

**Neurostimulatory approaches.** The neurostimulatory procedures include transcutaneous electrical nerve stimulation and invasive therapies—most importantly, spinal cord stimulation. The latter approach is considered most often for patients with refractory neuropathic pain.

**Table 20. Adjuvant analgesic agents**

<b>Drug class</b>	<b>Examples</b>
<b>Multipurpose analgesics</b>	
Antidepressants	
Tricyclic antidepressants	Amitriptyline, desipramine, imipramine, nortriptyline, doxepin
Selective serotonin reuptake inhibitors	Paroxetine, citalopram, fluoxetine, sertraline, fluvoxamine
Serotonin/norepinephrine reuptake inhibitors	Venlafaxine
$\alpha_2$ -Adrenergic agonists	Clonidine, tizanidine, dexmetomidine
Corticosteroids	Dexamethasone, prednisone, methylprednisolone
Topical analgesics	Capsaicin (eg, prilocaine/lidocaine cream, lidocaine 5% patch)
<b>Drugs used for neuropathic pain</b>	
All multipurpose analgesics	See drugs listed above
Anticonvulsant agents	Clonazepam (also a benzodiazepine), carbamazepine, gabapentin, phenytoin, valproate, lamotrigine, topiramate, trileptal
GABA agonists	Tiagabine
Oral local anesthetic agents	Mexiletine
NMDA receptor antagonists	Ketamine, dextromethorphan, amantadine, memantine
<b>Drugs used for musculoskeletal pain</b>	
Muscle relaxants	Methocarbamol, baclofen
Benzodiazapines	Diazepam, clonazepam
<b>Drugs used for headache</b>	
Nonsteroidal anti-inflammatory drugs	
Nonselective agents	Aspirin, ibuprofen, ketorolac, ketoprofen, naproxen
COX-2 selective agents	Celecoxib, rofecoxib, valdecoxib
Multipurpose analgesics	See drugs listed above
Anticonvulsants	See drugs listed above
<b>Drugs for vascular headache</b>	
Vasoactive drugs	Triptans (eg, sumatriptan, zolmitriptan, rizatriptan, naratriptan), ergots (eg, ergotamine, dihydroergotamine)
$\beta$ -Blockers	Propranolol, timolol, metoprolol, nadolol
Calcium channel blockers	Verapamil, diltiazem, nifedipine
Angiotensin-converting enzyme inhibitors	Captopril, enalapril

**Table 20. Adjuvant analgesic agents (continued)**

<b>Drug class</b>	<b>Examples</b>
Angiotensin II receptor blockers	Losartan, valsartan, irbesartan
<b>Drugs used for cancer pain</b>	
Drugs used for bone pain	
Corticosteroids	See drugs listed above
Calcitonin	Injectable and intranasal formulations
Bisphosphonates	Pamidronate, zoledronic acid, clodronate
Radiopharmaceuticals	Strontium Sr 89, samarium Sm 153
Drugs used for bowel obstruction	
Synthetic hormonelike drugs	Octreotide
Anticholinergic agents	Hyoscine, scopolamine
Corticosteroids	See drugs listed above

COX, cyclooxygenase; GABA, gamma-aminobutyric acid; NMDA, *N*-methyl-D-aspartate.

**Surgical neuroablative procedures.** Surgical therapies that isolate the painful part from the central nervous system are now rarely performed. The most widely used procedure, cordotomy (spinothalamic tractotomy), is sometimes considered in the setting of refractory cancer pain in the lower body. Neuraxial infusion techniques have largely replaced the need for surgical cordotomy.

**Physiatric techniques.** Many patients with painful conditions benefit from physical or occupational therapy, and the use of orthoses or prostheses in selected patients may have important analgesic consequences. Modalities used for analgesic purposes include heat and cold, vibration, and ultrasound.

**Psychologic approaches.** There is substantial evidence that cognitive therapies can have an analgesic effect in some populations of patients with chronic pain. These approaches include relaxation training, hypnosis, and biofeedback. Behavioral approaches may be useful to optimize function, which itself may have pain-reducing consequences.

**Complementary and alternative medicine (CAM) approaches.** CAM therapies are commonly pursued by patients. Some of these treatments have sufficient evidence to consider under the broad rubric of a multimodality therapeutic approach. Physicians often suggest a trial of acupuncture, therapeutic massage, chiropractic therapy, or movement or stretching therapies (eg, tai chi chuan, yoga). Several nutritional supplements, such as

**Table 21. Nonpharmacologic techniques to reduce the systemic opioid requirement**

<b>Approach</b>	<b>Type</b>	<b>Examples</b>
Anesthesiologic	Neuraxial infusion	Epidural or intrathecal infusion of local anesthetics and other drugs
	Neural blockade	Temporary nerve blocks, neurolytic blocks
	Injection therapies	Spinal injections, trigger point injections
Neurostimulatory	Superficial	Transcutaneous electrical nerve stimulation, counterirritation
	Invasive	Dorsal column stimulation
Surgical	Neurolytic lesions	Peripheral neurectomy, rhizotomy, cordotomy, and other lesions in brain or spinal cord
Physiatric	Orthoses/prostheses	Spinal or limb-bracing techniques
	Physical/occupational therapy	Therapeutic exercise
	Modalities	Heat, cold
Psychologic	Cognitive	Relaxation techniques, psychotherapy
	Psychoeducational	Structured support groups
Complementary and alternative medicine	Some nutraceuticals	Possibly glucosamine
	Acupuncture	
	Chiropractic therapy	
	Massage	

glucosamine, may have sufficient evidence to warrant recommendation. Other popular but untested therapies, including the so-called energy approaches such as craniosacral manipulation, treatments included under non-Western medical systems (eg, traditional Chinese medicine, Ayurvedic medicine), and unproven nutraceuticals or supplements, are not usually recommended as part of a conventional strategy for pain. If patients desire such treatments, however, and there is no evidence of a safety concern, it may be best to be supportive and to try to integrate all strategies into an approach focused on comfort and functional restoration.

**Suggested readings**

Indelicato RA, Portenoy RK. Opioid rotation in the management of refractory cancer pain. *J Clin Oncol* 2002;20:348-52

Mercadante S, Portenoy RK. Opioid poorly-responsive cancer pain. Part 1. Clinical considerations. *J Pain Symptom Manage* 2001;21:144-50

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Rowbotham MC, Twilling L, Davies PS, et al. Oral opioid therapy for chronic peripheral and central neuropathic pain. *N Engl J Med* 2003;348:1223-32