Opioid Analgesics for Pain Management: Critical Thinking to Balance Benefits & Risk

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Estimated time to complete this activity: 1.5 hours.

To complete the posttest and evaluation, visit www.unmc.edu/dept/cce/opioid_criticalthinking.htm (see page 12).
Please call 402.559.4152 or toll-free 877832.6924 with any questions.

Disclosures

Dr Fine is on the Advisory Board for Cephalon, Endo Pharmaceuticals, Lilly, and Merck; and is a Speaker for Cephalon.
Dr McCarrberg is on the Speaker’s Bureau for Endo Pharmaceuticals, Forest, Lilly, Merck, Pfizer, PriCara, and Purdue Pharma L.P.
Dr Passik is a Consultant for Alpharma, Cephalon, Endo Pharmaceuticals, and Ligand/King; receives Grants from Cephalon and Lilly;
and is on the Speaker’s Bureau for Cephalon and Ligand/King.
Dr Sinatra is a Consultant for Endo Pharmaceuticals, Upjohn-McNeil, and Merck and Company.
Dr Pasternak is on the Advisory Board and Speaker’s Bureau for Adolor Corporation, Cephalon, Endo Pharmaceuticals, EpiCept, J&J, Limerick
Neurosciences, Ortho-McNeil, and Sarentis.

Learning Objectives

At the conclusion of this activity, the participant will be able to:
1. Discuss factors affecting the selection of an opioid analgesic for individual patients.
2. Select appropriate patients for long-term opioid therapy.
3. Differentiate aberrant drug-related behaviors.

Practice Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Evidence</th>
<th>Source</th>
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<tbody>
<tr>
<td>Self-report should be the primary source of pain assessment when possible. (B)</td>
<td>B. There is evidence of types II, III, or IV, and findings are generally consistent.</td>
<td><a href="http://www.guideline.gov/s/summar...px?doc_id=3691">www.guideline.gov/s/summar...px?doc_id=3691</a></td>
</tr>
<tr>
<td>Opioid analgesic drugs may help relieve moderate to severe pain, especially nociceptive pain. Opioids for episodic (noncontinuous) pain should be prescribed as needed, rather than around the clock. Long-acting or sustained-release analogesic preparations should be used for continuous pain. Breakthrough pain should be identified and treated by the use of fast-onset, short-acting preparations. (IA)</td>
<td>Level I: Evidence from at least one properly randomized, controlled trial. A. Good evidence to support the use of a recommendation; clinicians “should do this all the time.”</td>
<td><a href="http://www.guideline.gov/s/summar...px?doc_id=3365">www.guideline.gov/s/summar...px?doc_id=3365</a></td>
</tr>
<tr>
<td>Patients taking analgesic medications should be monitored closely. Patients should be reevaluated frequently for drug efficacy and side effects during initiation, titration, or any change in dose of analgesic medications (IA)</td>
<td>Level I: Evidence from at least one properly randomized, controlled trial. A. Good evidence to support the use of a recommendation; clinicians “should do this all the time.”</td>
<td><a href="http://www.guideline.gov/s/summar...px?doc_id=3365">www.guideline.gov/s/summar...px?doc_id=3365</a></td>
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<tr>
<td>The clinician should watch for signs of opioid use for inappropriate indications (eg, anxiety, depression, grief, loss). Requests for early refills should include evaluation of tolerance, progressive disease, inappropriate behavior, or drug diversion by others. (IIIA)</td>
<td>Level III: Evidence from respected authorities, based on clinical experience, descriptive studies, or reports of expert committees. A. Good evidence to support the use of a recommendation; clinicians “should do this all the time.”</td>
<td><a href="http://www.guideline.gov/s/summar...px?doc_id=3365">www.guideline.gov/s/summar...px?doc_id=3365</a></td>
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<tr>
<td>Constipation and opioid-related gastrointestinal symptoms should be prevented. Assessment of bowel function should be part of the initial assessment and of every follow-up visit for all patients receiving analgesics. A prophylactic bowel regimen should be initiated with the commencement of persistent opioid therapy. (IA)</td>
<td>Level I: Evidence from at least one properly randomized, controlled trial. A. Good evidence to support the use of a recommendation; clinicians “should do this all the time.”</td>
<td><a href="http://www.guideline.gov/s/summar...px?doc_id=3365">www.guideline.gov/s/summar...px?doc_id=3365</a></td>
</tr>
<tr>
<td>Fixed-dose combinations of opioid with acetaminophen or NSAIDs may be useful for mild to moderate pain. The maximum recommended dose should not be exceeded, to minimize acetaminophen or NSAID toxicity. If a maximum safe (nontoxic) dose is reached without sufficient pain relief because of limits imposed by the maximum safe acetaminophen or NSAID dose, switching to noncombination preparations is recommended (IA)</td>
<td>Level I: Evidence from at least one properly randomized, controlled trial. A. Good evidence to support the use of a recommendation; clinicians “should do this all the time.”</td>
<td><a href="http://www.guideline.gov/s/summar...px?doc_id=3365">www.guideline.gov/s/summar...px?doc_id=3365</a></td>
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<table>
<thead>
<tr>
<th>Faculty</th>
<th>Perry G. Fine, MD</th>
<th>Steven D. Passik, PhD</th>
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<tbody>
<tr>
<td>Bill H. McCarrberg, MD (Chair)</td>
<td>University of Utah Salt Lake City, UT</td>
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<td>Gavril Pasternak, MD, PhD</td>
<td>Yale University School of Medicine New Haven, CT</td>
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<td>Raymond S. Sinatra, MD, PhD</td>
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Introduction
Chronic pain in America remains a prevalent, challenging, and expensive problem. A recent national telephone survey found that more than half of Americans live with chronic or recurrent pain. However, while 63% of Americans report having sought medical help for pain, fewer than half report that they have “a lot” of control over their pain, and fewer than one third had complete or a great deal of pain relief. The impact of pain is substantial, with 4 in 10 Americans reporting that pain interferes with their enjoyment of life, mood, sleep, and activities. In addition to affecting quality of life (QOL), pain also interferes with ability to work. The American Productivity Audit of more than 28,000 US workers found that lost productive time resulting from pain conditions costs employers $61.2 billion each year.

It is not surprising that pain is among the most common reasons for office visits, and that nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and nonopioid analgesics are among the most frequently prescribed therapeutic classes. When treating patients whose pain is not adequately managed with nonopioids, it is important that primary care physicians (PCPs) have sufficient knowledge of the pharmacology of opioids in order to prescribe them in a fashion that maximizes benefits and minimizes risk to patients.

Principles of Prescribing
Opioid Analgesics
When opioids are indicated for pain conditions not effectively managed by nonopioids, selecting an agent requires due consideration of a number of factors. The selection is based on the severity and pattern of pain; the patient’s age, medical comorbidities, and prior opioid exposure and experience (including efficacy and adverse effects); drug-specific differences; available formulations; cost; and personal experience. The availability of long-acting opioids has increased focus on the role of dosing intervals as a consideration in opioid therapy. Most short-acting opioids require a dosing interval of 4 to 6 hours; however, these may be favored initially because they are easier to titrate than long-acting opioids.

Although there is no evidence for the efficacy of one mu-opioid agonist over another in populations, individual patients may display a much better response to one drug over another, which is why consideration should be given to agents that the patient has found helpful in the past. A number of explanations for this interindividual response to opioids have been proposed.

Multiple Receptors
The 3 major opioid receptor families are mu, kappa, and delta. The primary site of action of most clinically used opioid
OPIOID ANALGESICS FOR PAIN MANAGEMENT

analgesics is the mu-opioid receptor, which is expressed at a spinal level in the dorsal horn and in multiple regions within the brain. The interindividual variability in response to mu-opioid analgesics can be explained in part by multiple mu-opioid receptors—splice variants—with different mechanisms of action and different distributions within a cell, regionally within the nervous system (brain and spinal cord), and in the peripheral nervous system.

Pharmacogenetics
The observed interindividual variability in response to opioids may be due in part to genetic polymorphisms. Studies have identified significant differences in the genotype of patients who required switching to alternative opioids compared with patients who responded to morphine. Response to an opioid depends on a number of factors, including drug absorption, distribution, metabolism, and elimination. Therefore a patient’s response to a particular opioid is potentially influenced by genetic variation in the alleles of several candidate genes. An example is the variable response to codeine in individuals with a polymorphism of the cytochrome P450 (CYP450) 2D6 gene, which prevents metabolism of the prodrug codeine to the active drug morphine. Up to 10% of people will have a poor analgesic response to codeine because they lack normal CYP2D6 activity. Morphine, although active alone, is also metabolized to a very active metabolite, morphine-6-glucuronide (MG6), chiefly through conjugation by uridine diphosphate glucuronyl transferase (UGT) enzymes. It has not yet been determined if polymorphisms in genes controlling the metabolism of morphine explain interindividual variability in response to morphine, but this may be related to patient characteristics such as age and renal and hepatic function. In patients with renal failure, accumulation of the pharmacologically active morphine metabolite MG6 may cause toxicity.

Drug Interactions
Most opioids are metabolized through the liver microsomal CYP450 system, which is responsible for the metabolism of a wide variety of drugs. Codeine, hydrocodone, methadone, oxycodone, and tramadol are chiefly metabolized through oxidative reactions by CYP2D6, while fentanyl, meperidine, and buprenorphine are metabolized by CYP2A4. Concomitant treatment with drugs that inhibit or induce CYP450 enzymes can alter the levels of these opioids and their metabolites; this may change their analgesic or side-effect profile and cause possible opioid overdose or acute withdrawal.

Morphine, hydromorphone, and oxymorphone are metabolized chiefly through conjugation reactions with UGT enzymes. Because they are not oxidatively metabolized by CYP450 enzymes, inhibition/induction or genetic polymorphisms of CYP450 enzymes should have little to no effect on the metabolism and clearance of these drugs.

Short-Acting Opioids
Short-acting opioids are available as single-entity agents or in combination with a nonopioid with a complementary mechanism of action (NSAIDs or acetaminophen). If pain is present for only a few brief periods during the day, patients may take an as-needed dose of a short-acting mu opioid. For persistent pain, a long-acting agent is recommended to control baseline pain around the clock and avoid breakthrough pain (BTP). But in most cases, a short-acting opioid is used to initiate and titrate around-the-clock therapy and, if necessary, as-needed dosing can be added to regular dosing in order to control or avoid BTP.

When initiating an opioid trial in an opioid-naïve patient, the dose should be individualized to the patient by starting at the lowest effective dose, which should be increased incrementally, with both the size of the increment and the interval between increments influenced by the degree of pain relief, functional improvements, and side effects experienced by the patient. Starting doses for common oral short-acting opioids to treat moderate to severe pain in opioid-naïve adults are shown in Table 1. A dose increment of 30% to 50% is safe and usually large enough to observe a meaningful change in analgesia. If pain is severe and the patient is not predisposed to opioid toxicity, a higher increment—up to 100% of the existing dose—may be considered. In ambulatory care, an additional consideration with regard to dose titration is the availability of an individual at home with the patient who is a reliable observer for potential adverse effects. An alternative approach in patients who receive additional as-needed opioids for BTP is to sum the amount of supplemental drug used per day during the previous few days and convert it into the fixed-schedule administration.

There is no predictable maximal therapeutic dose ("ceiling effect") for analgesia with single-entity opioid agonists, but dose-limiting adverse effects can occur. In contrast, the doses of opioids marketed in combination with a nonopioid are limited by the maximum dose of the nonopioid (eg, acetaminophen dose limit: 4 g per day in patients without compromised liver function or without a history of alcoholism). If significant adverse events occur before adequate analgesia is achieved, the dose may be reduced and the events should be treated. After a stable dose is achieved with a short-acting opioid, it may be converted to a long-acting opioid, for example, if there is a desire for a simplified regimen to optimize adherence, among other possible reasons.

Long-Acting Opioids
Long-acting opioids administered around the clock to treat persistent baseline pain can be given along with additional as-needed doses of short-acting opioids for exacerbations of pain (ie, BTP), to permit activity such as physical therapy, and for managed care, an additional consideration with regard to dose titration is the availability of an individual at home with the patient who is a reliable observer for potential adverse effects. An alternative approach in patients who receive additional as-needed opioids for BTP is to sum the amount of supplemental drug used per day during the previous few days and convert it into the fixed-schedule administration.

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<table>
<thead>
<tr>
<th>TABLE 1 Commonly Used Oral Short-Acting Opioids</th>
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<tbody>
<tr>
<td>Name</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Codeine</td>
</tr>
<tr>
<td>Hydrocodeine</td>
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<tr>
<td>Hydromorphone</td>
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<tr>
<td>Morphine</td>
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<tr>
<td>Oxycodone</td>
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<tr>
<td>Oxymorphone</td>
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<tr>
<td>Tramadol</td>
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*Reduce initial dose by up to 50% in frail, older patients and titrate upward based on therapeutic response and undesirable side effects. If deemed necessary to initiate therapy at a lower dose, patients may be started with 5 mg oxymorphone.

incident pain. Although many PCPs have not adopted the practice of using long-acting opioids for indications other than cancer pain, there are significant benefits from using these agents for long-term pain, including improved control of baseline pain and the need for smaller quantities of pills. The most commonly used long-acting opioids are sustained-release (SR) preparations of short-acting opioids. Some SR opioids can be initiated in opioid-naïve patients, although not all have been systematically evaluated as an initial agent, and most experts would recommend starting a short-acting agent before using a long-acting agent (TABLE 2). Once initiated, the long-acting opioid dose can also be titrated by incorporating the as-needed short-acting doses into the daily long-acting dose. Patients should be advised to swallow SR oral opioid formulations whole, and not to break, crush, or chew tablets in order to prevent the rapid release of potentially dangerous opioid levels (refer to prescribing information for individual agents). Some formulations also have warnings regarding use with alcohol that can cause “dumping” of the opioid content all at once, rather than in a sustained fashion.

Managing Adverse Effects

Treatment of opioid-induced side effects is integral to opioid pain management. A number of adverse effects are associated with the use of opioid analgesics. The most common are opioid-induced bowel dysfunction (constipation), sedation, nausea and vomiting, pruritus, sweating, dry mouth, and weakness. Other adverse effects include respiratory depression, urinary retention, confusion, hallucinations, nightmares, myoclonus, dizziness, dysphoria, and the very rare hypersensitivity reaction of anaphylaxis. With the exception of bowel dysfunction, tolerance often develops rapidly to some of the common opioid-related side effects, such as nausea and vomiting. Therefore, routine prophylactic administration of an antiemetic agent is not typically indicated, except in patients with a history of severe opioid-induced nausea. Opioid-induced bowel dysfunction should be anticipated and treated prophylactically with a stimulating laxative to increase bowel motility, with or without stool softeners as indicated by stool consistency.

Nonpharmacologic approaches for all patients include:
- Increase fluid intake as tolerated.
- Increase dietary fiber as tolerated (unless patient is severely debilitated or bowel obstruction is suspected).
- Encourage mobility and ambulation if appropriate.
- Ensure comfort and privacy for defecation.
- Encourage bowel movements at the same time each day.
- Rule out or treat impaction.

TABLE 3 shows examples of the pharmacologic management of common opioid-induced adverse effects. In some patients who poorly tolerate one opioid, it may be necessary to change to a different opioid.

Incomplete Cross-Tolerance

Patients often exhibit limited cross-tolerance when one opioid is substituted for another, which might reflect their differing selectivities for the mu-opioid receptor subtypes (mu-opioid receptor splice variants). Clinicians have long made use of the incomplete cross-tolerance among mu-opioid analgesics by using the concept of opioid rotation, in which highly tolerant patients are rotated to a different drug to regain analgesic sensitivity. Incomplete cross-tolerance among opioids affects the conversion from one opioid to another. When switching between opioids in an opioid-tolerant patient, it is recommended to calculate the equianalgesic dose based on the predicted

<table>
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<th>TABLE 2</th>
<th>Long-Acting Opioids</th>
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<tbody>
<tr>
<td><strong>Fentanyl</strong></td>
<td></td>
</tr>
<tr>
<td>Duragesic&lt;sup&gt;a&lt;/sup&gt;</td>
<td>q72h</td>
</tr>
<tr>
<td><strong>Methadone</strong>: Use not recommended without significant expertise. Repeated administration at short intervals may lead to accumulation in plasma and delayed adverse effects because the prolonged half-life is greater than the duration of analgesia.</td>
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<tr>
<td><strong>Morphine</strong></td>
<td></td>
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<tr>
<td>Avinza&lt;sup&gt;a&lt;/sup&gt;</td>
<td>q24h</td>
</tr>
<tr>
<td>Kadian&lt;sup&gt;a&lt;/sup&gt;</td>
<td>q12 or q24h</td>
</tr>
<tr>
<td>MS Contin&lt;sup&gt;b&lt;/sup&gt;</td>
<td>q12h</td>
</tr>
<tr>
<td>Oramorph SR&lt;sup&gt;c&lt;/sup&gt;</td>
<td>q12h</td>
</tr>
<tr>
<td><strong>Oxycodone</strong></td>
<td></td>
</tr>
<tr>
<td>OxyContin&lt;sup&gt;c&lt;/sup&gt;</td>
<td>q12h</td>
</tr>
<tr>
<td><strong>Oxymorphone</strong></td>
<td></td>
</tr>
<tr>
<td>Opana ER&lt;sup&gt;c&lt;/sup&gt;</td>
<td>q12h</td>
</tr>
</tbody>
</table>

<sup>a</sup> Individualize dose for each patient; <sup>f</sup> Not approved for initiation of therapy—advisable to begin treatment with immediate-release opioid.
equivalent dose in conversion tables, which were determined by relative potency studies in opioid-naïve patients, and then cut the calculated dose by at least 50% in order to account for incomplete cross-tolerance. Using this method, shortfalls in efficacy for the sake of safety can be compensated for in the short term by using immediate-release (IR) opioid (“rescue”) doses, with corrections in around-the-clock dosing determined after steady state is achieved with the new drug, which requires 3- to 5-times the half-life of the drug.

**Patient Selection for Long-Term Opioid Therapy**
Most patients with pain do not need opioids, but such therapy may be required to effectively control moderate to severe pain. However, recent reports suggest that certain populations receiving long-term opioid therapy are particularly at risk for poor outcomes. It is certainly true that poor patient selection for opioid therapy, opioid monotherapy in the absence of comprehensive management, and inadequate follow-up of patients can be detrimental to patients. At the same time, most PCPs have some experience of treating patients for whom opioid therapy is appropriate and effective, with good long-term outcomes. Because the potential long-term benefits of chronic opioid therapy can be contentious, careful patient selection, comprehensive management, and appropriate follow-up are crucial.

Opioids alone are not the optimal therapy, but when used in conjunction with nonopioid analgesics, such as an NSAID or adjuvant, and psychologic and physical approaches, they can help to maximize patient outcomes. For certain populations, such as chronic back pain and headache patients, and those with a personal or family history of substance abuse, some PCPs may decline to prescribe opioids or defer initiating opioid therapy until specialist evaluation and support is obtained. When opioid treatment is warranted, a treatment plan should state objectives that will be used to determine treatment success, such as pain relief, improved physical and psychosocial function, manageable side effects, and drug-taking that follows the rules of appropriate behavior.

**Assessing Pain**
Selecting patients for long-term opioid analgesic therapy requires a comprehensive assessment of pain, including obtaining, evaluating, and documenting a thorough medical history and physical examination, as well as patient and disease characteristics. Because pain is inherently subjective, patient self-report is the “gold standard” for assessment. Pain assessment should focus on the type and quality of pain, source, intensity, location, duration/time course, associated factors that exacerbate or relieve pain, pain affect, and effects on lifestyle and functional status. Numerous tools are available to measure pain intensity, such as the verbal rating scale, the visual analog scales, and the faces of pain scale. These tools are simple to use and sensitive enough to detect changes that occur during pain treatment.

As well as the nociceptive input, pain can also be composed of psychologic and emotional overlays, such as anxiety, depression, and fear. Analgesics such as opioids, however, are only effective in reducing pain intensity, and will not address other aspects of patients’ pain experiences. If the PCP suspects these conditions are present, it is important to assess and address these domains at the same time as the nociceptive pain. This may be necessary at the initial visit, or there may be no indications of a problem until a subsequent visit or, for example, after an early refill request. Several short, accurate, and easy-to-use instruments to detect depression are available such as Beck Depression Inventory.

<table>
<thead>
<tr>
<th>TABLE 3</th>
<th>Pharmacologic Interventions for Opioid Adverse Effects</th>
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<tbody>
<tr>
<td><strong>Adverse effects</strong></td>
<td><strong>Examples of pharmacologic interventions</strong></td>
</tr>
<tr>
<td>Intermittent use (q2-3d) of osmotic laxative</td>
<td>Magnesium hydroxide, magnesium citrate, sodium phosphate</td>
</tr>
<tr>
<td>Trial of daily softening agent alone</td>
<td>Sodium docusate</td>
</tr>
<tr>
<td>Intermittent use (q2-3d) of contact cathartic</td>
<td>Senna, bisacodyl</td>
</tr>
<tr>
<td>Daily use of cathartic preparation (as softening agent)</td>
<td>Senna, bisacodyl</td>
</tr>
<tr>
<td>Daily use of lactulose or sorbil</td>
<td>Daily use of polyethylene glycol</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>Neuroleptics Prochlorperazine, chlorpromazine, haloperidol</td>
</tr>
<tr>
<td></td>
<td>Anticholinergic drugs Scopolamine</td>
</tr>
<tr>
<td></td>
<td>Antihistamines Promethazine, meclizine, diphenhydramine, dimenhydrinate, hydroxyzine, trimethobenzamide</td>
</tr>
<tr>
<td></td>
<td>Prokinetic drugs Metoclopramide</td>
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<tr>
<td></td>
<td>Corticosteroids Dexamethasone</td>
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<tr>
<td></td>
<td>Benzodiazepines Lorazepam</td>
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<tr>
<td></td>
<td>Cannabinoids Dronabinol</td>
</tr>
<tr>
<td></td>
<td>5-HT3 receptor antagonists Ondansetron, granisetron, dolasetron</td>
</tr>
<tr>
<td>Somnolence and cognitive impairment</td>
<td>Psychostimulants Methylphenidate, dextroamphetamine, modafinil</td>
</tr>
<tr>
<td>Myoclonus*</td>
<td>Low-dose benzodiazepines Clonazepam</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Baclofen</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Antihistamines Diphenhydramine, hydroxyzine</td>
</tr>
<tr>
<td>Sedative hypnotics</td>
<td>Lorazepam</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>Paroxetine</td>
</tr>
</tbody>
</table>

*Adjust dose and dosing schedule of selected therapy to optimize effects. Switch or combine conventional approaches if initial therapy is inadequate;

Zung Self-Depression Scale). Brief instruments, including asking the patient 2 questions about the presence of depressed mood and anhedonia (“Over the past 2 weeks, have you felt down, depressed, or hopeless?” and “Over the past 2 weeks, have you felt little interest or pleasure in doing things?”), appear to perform as well as longer instruments.25

Information about medical and surgical conditions, history of chronic pain, and previous pain treatments is also important.7 Identifying the etiology, syndrome, or pathophysiology of pain can help guide the selection of treatment and suggest the prognosis.7

**Assessing Risk**

The potential for misuse, abuse, and addiction should be addressed when considering long-term opioid analgesic treatment. Assessing risk is not intended to deny high-risk patients treatment for their pain, but rather to match the degree of clinical monitoring and controls to the degree of risk in order to achieve better clinical outcomes and minimize misuse. There are many ways to assess risk, including a psychiatric interview and the use of one or more of an increasing number of screening tools (eg, Opioid Risk Tool [ORT], Screener and Opioid Assessment for Patients with Pain [SOAPP], DIRE score). Such tools should be used by clinicians, for example, when considering initiating opioid analgesic therapy for a chronic pain problem or for a patient being treated with opioids for an acute pain problem that is becoming chronic and long-term opioid therapy is an option. A patient who displays an aberrant drug-related behavior that raises concern (eg, requests an early opioid refill) or does not seem to be doing well requires attention, such as asking him or her to come in to complete a screening tool for addiction, social problems, or other psychologic distress, rather than automatically writing a refill.

**Informed Consent**

It is an ethical and often regulatory duty to describe in understandable terms the risks and benefits of the use of long-term opioid analgesic therapy with the patient or persons designated by the patient. The physician can consider the use of a written agreement outlining the treatment plan, expectations, and the responsibilities of the patient and physician. Although physicians often feel uncomfortable asking patients to sign an agreement, a signed plan of care is particularly important if the patient is at high risk for medication abuse, and may be required in some states. It is also important to outline the procedures or actions that will be taken should problems arise and the patient does not adhere to the terms of the agreement.

A sample opioid treatment agreement is available at the American Academy of Pain Medicine Website: www.painmed.org/productpub/statements/pdfs/controlled_substances_sample_agmt.pdf. Clinicians should take care to follow the guidelines in the written agreements that they utilize or they risk exposing themselves to potential liability. They should adapt an agreement so that the language provides flexibility for them to make clinical decisions when managing patients (eg, “Early refills will generally not be given”).

**Individualized Therapy**

Clinical treatment of pain with opioids requires individualization of therapy, due to variability in efficacy, side effects, tolerance profiles, and risk of drug abuse among patients. Some patients may respond far better to one mu opioid than to another with respect to both analgesia and side effects. For example, patients unable to tolerate morphine due to severe nausea/vomiting may be able to take another mu agonist without a problem. Patients also vary in their sensitivity to a specific opioid, with some needing higher or lower doses to achieve optimal analgesia. At present, it cannot be predicted which patients are likely to achieve adequate analgesia or develop intolerable adverse effects from a given opioid, and in clinical practice, therapy often needs to be switched from one opioid to another to identify the most effective. The availability of a wide variety of opioids allows clinicians to better match the drug to the patient. Increased options become available when novel opioid analgesic molecules are developed and when existing drugs are reformulated into different delivery systems (eg, transdermal delivery system, SR oral tablet) or have a different mode of administration (eg, patient-controlled analgesia, computer-assisted delivery).

**Periodic Review**

Patients should be monitored regularly to assess their response to therapy, to identify and manage side effects, and to identify and manage aberrant drug-related behavior. The frequency of follow-up should be as often as clinically necessary and in compliance with state regulations, where present. Continuation or modification of controlled substances for pain management therapy depends on the evaluation of progress toward treatment objectives. The “Four As” of pain medicine will help to direct therapy and support the pharmacologic options taken (Table 4). The “Four As” serve as a mnemonic device to remind clinicians that a successful outcome in pain therapy involves more than lowering pain scores. Equally important outcomes include stabilization or improvement in psychosocial functioning and sleep, tolerable side effects, optimization of physical functioning, and absence of aberrant behaviors.

Urinary drug testing can be an important tool to assist in monitoring adherence to a treatment plan when managing patients receiving opioid therapy. Controversies exist regarding their clinical value, partly because many current methods are designed for, or adapted from, forensic or workplace deterrent-based testing for illicit drug use. As a result, they are not necessarily optimized for clinical applications where a number of licit prescription drugs must also be included. However, when used with an appropriate level of understanding, urine drug testing can improve a physician’s ability to manage therapy with opioids and identify substance misuse.

As more PCPs prescribe opioid analgesics for the management of chronic moderate to severe pain, the questions of how to monitor adherence to the therapeutic regimen and when to refer a patient for additional evaluation and treatment in order to achieve treatment objectives have become important issues.

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**TABLE 4** The “Four A’s” of Pain Medicine

<table>
<thead>
<tr>
<th>Analgesia (meaningful pain relief)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activities of daily living (stabilization &amp; improvement in psychosocial function &amp; specifically identified functional [physical activity] goals)</td>
</tr>
<tr>
<td>Adverse effects (side effects)</td>
</tr>
<tr>
<td>Aberrant drug-related behaviors (adherence to plan of care &amp; addiction-related outcomes)</td>
</tr>
</tbody>
</table>

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In general, referral to a pain specialist or pain center is appropriate when the clinician has exceeded his or her expertise in any specific area of opioid-related pain management. Reasons may include the dose of opioids prescribed, the patient’s inability to adhere to the prescribed regimen, an inability to achieve adequate pain control despite increasing the dose or switching to different opioids, unresolved troublesome side effects, or unresolved issues of substance misuse. Special attention should be given to patients who are at high risk for medication misuse, abuse, or diversion, and especially those with a known history of drug addiction.

Differentiating Aberrant Drug-Related Behaviors

No behavior is absolutely predictive of addictive disease, and these behaviors exist along a continuum, with certain behaviors being less problematic and others being more so (TABLE 5). Other explanations for nonadherent behavior include untreated pain, psychologic distress, and addiction. It is important that clinicians can distinguish between physical dependence, addiction, and tolerance (TABLE 6), so that they do not incorrectly assume that a patient is addicted.

Aberrant behaviors are not to be ignored, but do not mean that prescribing should be immediately discontinued. Clinicians should proceed with caution, set limits, be thoughtful, and react therapeutically. The syndrome of drug-seeking behaviors that arises when a patient cannot obtain adequate relief with the prescribed dose of analgesic and seeks alternate sources or increased doses of analgesic is referred to as pseudoaddiction. This may be the result of increasing pain due to disease progression, development of a new condition, or inadequate instruction or dose provision by the clinician.

Psychiatric factors, such as anxiety or depression, a personality disorder, or changes in cognitive state, such as mild encephalopathy due to the treatment regimen of medical comorbidities or underlying psychiatric problems, may be responsible for the behaviors identified. The pain patient who escalates his or her opioid dose to self-medicate untreated anxiety, depression, or insomnia bears resemblance to addiction with regard to how the drug and drug procurement becomes a central part of the patient’s life. Such patients who use chemicals to cope with adverse life situations (also known as “chemical copers”) need structure, psychiatric input, and drug treatments that decentralize the pain medication to their coping and prevent maladaptive opioid analgesic use.

Changing Course: Discontinuing Opioid Therapy (“Exit Strategy”)

Long-term opioid therapy may need to be discontinued for a number of reasons, including when opioids are no longer effective for pain or to improve function, when unacceptable side effects or toxicity occur, or when patients violate the opioid treatment agreement or display certain aberrant drug-related behaviors. When it is necessary to discontinue treatment, withdrawal symptoms can usually be avoided by use of a slow opioid tapering schedule (reducing the dose by 10% to 20% each day or more slowly if symptoms occur). Anxiety, tachycardia, sweating, and other autonomic symptoms that persist may be lessened by slowing the taper or using clonidine at an oral dose of 0.1 to 0.2 mg/day. The use of buprenorphine for both pain and opioid dependence in the primary care office is increasingly common, but requires certification under the Drug Addiction Treatment Act of 2000.

### TABLE 5

**Examples of Aberrant Drug-Related Behaviors**

<table>
<thead>
<tr>
<th>Less indicative of addiction</th>
<th>More indicative of addiction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug hoarding during periods of reduced symptoms</td>
<td>Prescription forgery</td>
</tr>
<tr>
<td>Acquisition of similar drugs from other medical sources</td>
<td>Concurrent abuse of related illicit drugs</td>
</tr>
<tr>
<td>Aggressive complaining about the need for higher doses</td>
<td>Recurrent prescription losses</td>
</tr>
<tr>
<td>Unapproved use of the drug to treat another symptom</td>
<td>Selling prescription drugs</td>
</tr>
<tr>
<td>Unsanctioned dose escalation 1 or 2 times</td>
<td>Multiple unsanctioned dose escalations</td>
</tr>
<tr>
<td>Reporting psychic effects not intended by the clinician</td>
<td>Stealing or borrowing another patient's drugs</td>
</tr>
<tr>
<td>Requesting specific drugs</td>
<td>Obtaining prescription drugs from nonmedical sources</td>
</tr>
</tbody>
</table>

### TABLE 6

**Definitions of Addiction, Physical Dependence, Tolerance, and Pseudoaddiction**

**Addiction**: A primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.

**Physical dependence**: A state of adaptation that is manifested by a drug-class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.

**Tolerance**: 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.

**Pseudoaddiction**: An iatrogenic syndrome of behaviors developing in direct consequence of inadequate pain management. The natural history of pseudoaddiction is a progression through 3 characteristic phases including: (1) inadequate prescription of analgesics to meet the primary pain stimulus; (2) escalation of analgesic demands by the patient associated with behavioral changes to convince others of the pain’s severity; and (3) a crisis of mistrust between the patient and the health care team.
Case Studies
The following case studies illustrate the application of the principles of prescribing opioids for pain management, ranging from a simple acute case through to more complex patients with chronic pain and psychologic dysfunction. Although there is no question that physicians should seek consultation when needed, such a requirement is not necessary for every case, especially if the practitioner is knowledgeable about pain management. PCPs have varying levels of comfort, knowledge, and experience in the treatment of chronic pain, which will affect the threshold for obtaining consultation or referral for each patient. Furthermore, the availability of pain specialists, pain management programs, and addiction disease specialists varies widely depending on practice location and resources.

The Case of Mr K: A 25-Year-Old Man With Acute Ankle Sprain
Mr K, a 25-year-old male patient of yours for 6 years, presents in significant pain with a traumatic acute ankle sprain that occurred while playing recreational tennis 2 days ago. Since the injury, he has been taking NSAIDs regularly, rested and kept the foot elevated when possible, and used ice to reduce the swelling. He has missed 2 days of work as an architect and is anxious to return as soon as possible.

History
- No prior history of ankle pain or any chronic musculoskeletal problems, apart from a broken wrist several years ago.
- He is otherwise healthy and is taking no medication other than the NSAID.

Physical Examination
- Well-developed, thin male in apparent discomfort.
- Localized pain that is increased upon ankle inversion.
- Able to bear weight with attendant pain rated at 7-8/10.
- Swelling is present.
- Findings suggest a second-degree sprain.

What Next?
- Continue ice and elevation, but add gradual motion and motility with use of an ankle support. Achilles tendon stretching should begin 48 to 72 hours after ankle injury since tissues contract after trauma with immobility.
- Hydrocodone/acetaminophen 5 mg/500 mg 20 tablets, q4-6h.

Outcome:
- Mr K presents at the follow-up visit in 2 weeks able to walk with care without opioid analgesia, with only mild pain.
- Two hydrocodone/acetaminophen 5 mg/500 mg tablets are left.
- He has returned to his employment as an architect, with temporary modifications to minimize his need to walk.
- Advise him to continue a progressive physical therapy (PT) program, and caution him that full strength may not return for a number of months.

The Case of Mrs T: A 60-Year-Old Woman With Osteoarthritis of the Knees
Mrs T is a 60-year-old woman with osteoarthritis (OA) who has been your patient for many years. She has progressively increasing pain in her knees, rated at 7/10 with activity, for which she currently takes around-the-clock naproxen and acetaminophen. She has been at the maximum acetaminophen and NSAID doses for 7 months, and although initially alleviating her symptoms, this regimen no longer controls her pain with activity, and she feels restricted in what she is able to do.

Past Medical History
- Mrs T had an acute myocardial infarction (MI) 2 years ago, following which she experienced major depression, which was treated to remission with fluoxetine.
- Hysterectomy 3 years ago.
- A 5-year history of OA of the knee. You previously recommended weight reduction and physical exercise, which she complied with (losing 5 lbs), but she is finding it difficult to complete her exercise regimen (45 minutes cardio and strength training, 4 times a week).
- Knee injections by an orthopedic specialist provided only short-term relief.
- No allergies.

Medication Use
- Naproxen and acetaminophen.
- Glucosamine sulfate and chondroitin sulfate supplements.
- Timolol maleate 10 mg q12h.
- ASA 81 mg + multivitamin q24h.

Family History
- Her father died of an MI at age 63 years and her mother died of “old age.”
- She has no siblings.
Psychosocial History
Mrs T works part-time (2 days per week) as a bookkeeper. Her husband is retired, but their investment income is comfortable; they have comprehensive medical insurance.
One son lives out of state.
She does not use alcohol.
She is unwilling to consider evaluation for joint replacement.

Physical Examination
Mrs T is a pleasantly interactive, slightly overweight female in no acute distress.
She is fully cooperative with the history and physical examination.
Pain with limited range of motion (ROM) in both knees.

What Next?
Discontinue naproxen.
Initiate IR tramadol at 25 mg/day qAM, titrate in 25 mg increments as separate doses every 3 days to reach 100 mg/day (25 mg q6h), and increase by 50 mg every 3 days to reach 200 mg/day (50 mg q6h).

One Week Later
Pain control is good, but to provide a more convenient regimen you switch Mrs T to SR tramadol, 200 mg q24h.

Interim Phone Call
Pain control and function are good.
Mrs T is experiencing tremors and has become hypertensive.
Initiate SR oxymorphone 5 mg q12h, with instructions to increase the dose to 10 mg q12h after 3 days if pain is not adequately controlled.
Prescribe IR oxymorphone 5 mg to use as needed prior to exercising.
Ask her to call the office in 5 days to review her need for supplemental oxymorphone.
Prescribe a stimulating laxative to prevent constipation.

Interim Phone Call
Pain was well controlled with oxymorphone 10 mg q12h—she used 1 IR oxymorphone 5 mg tablet about an hour prior to going to the gym 4 days a week, and occasionally if her pain was exacerbated (2 to 3 times a week).
Bowel function is normal.

Two Months Later
Mrs T is doing well on her current regimen (SR oxymorphone 10 mg q12h with IR oxymorphone 5 mg [30 tablets/month]). She is not experiencing adverse effects and is able to work and to exercise.
Continue her regimen and schedule a follow-up appointment for 2 months.

The Case of Mrs J: An 82-Year-Old Woman With Osteoarthritis
Pain from OA has been present in Mrs J’s hips, knees, ankles, and shoulders for more than 10 years, for which occasional use of NSAIDs (ibuprofen, naproxen) had been sufficient. However, her pain intensity with activity is now 6/10, and she experiences increasing dyspepsia with NSAID use.

Past Medical History
Osteoporosis with degenerative disk disease (no vertebral fractures).
Type 2 diabetes mellitus managed with diet alone.
Hysterectomy for fibroids.
Mild dementia from Alzheimer’s disease.

Medication Use
NSAIDs.
Glucosamine sulfate and chondroitin sulfate supplements.
Alendronate.
Donepezil 5 mg q24h.
ASA 81 mg + multivitamin q24h.

Family History
Both parents died of “old age.” Her mother was in considerable pain, “all bent over” for many years. Her father used a cane and had trouble walking from “arthritis.”
■ Her sister died of uterine cancer.
■ Her brother had coronary artery bypass graft surgery at age 57 years and died of a cerebrovascular accident at age 68 years.

**Psychosocial History**
■ Mrs J graduated from teacher's college and taught until motherhood.
■ Her husband died suddenly 8 years ago of an acute MI and she lives alone on a fixed income from Supplemental Security Income (SSI) and her husband's annuity; basic living expenses are covered, but not much is left over.
■ One daughter lives close by and is supportive, and 2 children live out of state.
■ Relies on Medicare supplemental insurance (co-pay: $25 for brand drugs, $10 for generics).
■ She does not use alcohol.
■ She has no living will or written advanced directives.

**Review of Systems**
■ Progressive short-term memory loss, occasional confusion, and increasing difficulty with routine tasks.
■ No chest pain, dyspnea at rest, melena, or hemoptysis.
■ Sleep, mood, and bowel/bladder function unremarkable.

**Physical Examination**
■ Well groomed, in no obvious distress.
■ Alert and oriented to time, place, person, and objects, but unable to subtract “serial 7s” and could not recall 3 objects.
■ No visual or hearing changes, normal gait and balance.
■ No cardiac, peripheral vascular, or pulmonary problems.
■ Kyphosis of the spine, but no localized tenderness or tender points.
■ Limited ROM in the spine and joints, but no erythema or swelling.

**Description of Pain**
■ Dull and constant, with sharp exacerbations in the low back, knees, and hips with walking, bending, or prolonged standing.
■ No radicular complaints, burning, paresthesias, loss of grip strength, or loss of bowel or bladder control. Findings are suggestive of nociceptive pain due to moderate to advanced OA without a neuropathic component.

**What Next?**
■ Discontinue NSAIDs.
■ Initiate acetaminophen 1 g q6h.
■ Recommend “arthroswim” through the Arthritis Foundation Aquatic Program.

**Interim Phone Call**
■ Pain is 1/10 at rest and “tolerable” (3-4/10) with activity.
■ Mrs J is reluctant to travel to her YMCA for arthroswim. Warm baths feel good and help her sleep. You suggest that she exercise when pain and stiffness are minimal (eg, after a warm bath or application of superficial moist heat).

**Two Months Later**
■ Pain has increased to 8/10 with activity and she has difficulty sleeping:
  “I can’t get comfortable.”
■ She is experiencing difficulties with self-care and mood disturbance:
  “I don’t care about anything anymore.”
■ Initiate 200 mg celecoxib q24h.

**Two Weeks Later**
■ Pain is improved, with no apparent adverse events, but still keeps her less active than she would like.
■ Her daughter reports that Mrs J’s mood, sleep, energy, self-care, and general appearance seem better, but she cringes with activity and pain is “intolerable” when walking.

**What Next?**
■ Discontinue celecoxib and initiate tramadol 25 mg qAM, increased by 25 mg every 3 days to 100 mg/day (25 mg q6h) and by 50 mg every 3 days to 200 mg/day (50 mg q6h).
■ Convert IR tramadol to SR tramadol 200 mg q24h.

Acetaminophen carries a lower risk of GI complications than NSAIDs. It should be considered early in the management of OA pain because of its safety profile at daily doses not exceeding 4 g (avoid in patients with chronic alcohol abuse and use with caution in patients with liver disease). Recent data suggests elevated alanine aminotransferase levels in healthy adults receiving 4 g daily, but the transient elevations usually resolve with continued acetaminophen treatment, and are not accompanied by signs of liver injury.

Consider a physical activity program for all older patients that includes exercises to reduce stiffness and improve flexibility, ROM, strength, and endurance.

Chronic pain can have a tremendous psychologic impact and can lead to both physiologic and emotional decline.

Select celecoxib because of a history of GI intolerance with nonselective NSAIDs.

Rather than increase the celecoxib dose to 200 mg bid (because of GI, renal, and cardiovascular risk), you select opioid therapy. Opioids are recommended when moderate to severe OA pain not controlled by other treatments affects the patient’s QOL. You select single-entity tramadol, a weak mu-opioid agonist and inhibitor of serotonin and norepinephrine reuptake, to add to her current acetaminophen as the combination product is more expensive.

Although more expensive, the long-acting agent taken once daily will simplify dosing.
One Year Later

- She is experiencing exacerbation and progression of her OA. Pain is minimal at rest, but is “real bad” in the low back, hips, and lower extremities after walking 50 feet: “My legs feel like rubber...like they’re someone else’s.”
- Good tissue perfusion and pulses; no focal neurologic signs, atrophy, or tender points.
- She sleeps well, but feels stiff in the morning.
- Exerts all her time and energy performing basic ADLs.
- Blood pressure remains high normal.
- She has developed neurogenic claudication secondary to probable spinal stenosis.
- The daughter reports more confusion, occasional disorientation, and forgetfulness about medicine. She is worried about Mrs J’s ability to care for herself.

What Next?

- Review goals of therapy with Mrs J and her daughter.
- A series of epidural injections were not beneficial.
- Discuss surgery, but the daughter wants to manage the patient medically.
- Discontinue tramadol; initiate SR morphine 15 mg q12h.
- Initiate a prophylactic bowel regimen with a senna stimulant and stool softener. Encourage adequate diet and fluid intake, regular toileting habits, and physical activity. Advise her to avoid bulking agents, which should be used with caution in patients who are immobile and with questionable hydration.
- Remind the daughter to check on adherence to the bowel regimen.

Several Months Later

- Incident pain is worsening and unremitting after any amount of standing or walking.
- Pain in the low back is 5-6/10, nonradiating at rest but referred down her legs with activity. Mrs J believes that morphine has “stopped working” and makes her “feel bad.”
- The daughter notices some twitching in her hands.
- No problems with bowel/bladder function or changes in muscle strength.
- Discontinue SR morphine, initiate SR oxycodone 20 mg q12h.
- Oxycodone IR 5 mg prior to activities that incite breakthrough pain (BTP).

One Year Later

- Mrs J did well for the first few months of SR opioid therapy with IR medications, rating her pain as 3/10 on average, but has gradually required increased doses to maintain pain control and function (currently SR oxycodone 20 mg q8h).
- She is forgetting doses and the resulting pain interferes with self-care. Her daughter worries that Mrs J will take too little oxycodone and suffer or take too much and overdose.
- Mrs J is losing memory and struggles with simple tasks. While there is still cognitive capacity for decision-making, you discuss advance directives and review goals of therapy, her living situation, and what to expect as Alzheimer’s disease progresses. You emphasize the importance of pain evaluation and control because of the adverse effects on neuropsychologic and physical function.
- Discontinue SR oxycodone and initiate transdermal fentanyl 25 µg q72h. After 3 weeks increase dose to a 50 µg fentanyl patch (using 12 µg patches for dose titration).
- Instruct the daughter to evaluate her mother’s verbal and behavioral responses to activity and supplement “pre-treat” with oxycodone IR as needed. She leaves one 10 mg oxycodone/325 mg acetaminophen tablet available to her mother and checks on her throughout the day to replace it, if necessary.

Long-Term Outcome

Several months later, Mrs J moves in with her daughter. Home hospice care is initiated when she progresses to end-stage Alzheimer’s disease. Pain control is maintained with transdermal fentanyl and oxycodone solution for BTP for her remaining 2 weeks.
The Case of Mr A: A 45-Year-Old Man With Low Back Pain

Mr A is a 45-year-old male with pain in the low back radiating into the right buttock for many years. He is new to your practice requesting a refill of hydrocodone/acetaminophen 5 mg/500 mg, which he began 7 months ago because he was experiencing increasing dyspepsia with regular use of NSAIDs. His pain intensity with activity is 8/10, prohibiting him from working or participating in other activities; he is able but sometimes unwilling to perform ADLs.

Oral Medical History
- After a back injury at work 6 years ago, he went through extensive workup including multiple courses of PT, physical medicine review, anesthetic procedures, and acupuncture.
- MRIs have shown “3 bulging discs and a narrow canal.”
- His medical history is otherwise remarkable only for hypertension.
- He has tried codeine/acetaminophen 60 mg/300 mg q6h, several NSAIDs, lidocaine patch 5%, gabapentin 600 mg q8h, and amitriptyline 25 mg qhs, but claims they all stopped working or he was unable to tolerate them.
- His current medication regimen is atenolol 50 mg q24h and hydrocodone/acetaminophen 5 mg/500 mg 2 q6h.

Family and Psychosocial History
- His father had an MI at age 65 years and is still living. He is an alcoholic who would return from the bar after work and beat the patient as a child.
- His mother died of breast cancer 6 years ago. She was submissive to the husband’s aggressive behavior and was withdrawn and anxious.
- Two children in their early 20s live locally—one has undergone drug rehabilitation and the other uses no alcohol.
- Mr A used marijuana frequently as a teenager. He currently smokes cigarettes, drinks 2 beers a day, and occasionally the “hard stuff.” Alcohol and “Vicodin” help his “nerves.”
- He lives with his wife, relying on a modest fixed income from SSI and her income; his wife resents his lack of employment.

Review of Systems
- Blood pressure is 135/85.
- Sleep is “poor” and the patient states his mood is “okay,” but looks depressed.

Physical Examination
- The patient is not well groomed and has a ruddy complexion.
- He answers in short sentences and seems in a hurry to leave with his hydrocodone prescription.
- The exam is unremarkable except for mild tenderness to light touch over the midline of the back from L3-S1 and mild tenderness in the right SI joint. Normal reflexes, strength, and sensations; no atrophy noted. Normal straight leg raise and normal but slow gait.

What Next?
- Administer the Opioid Risk Tool (ORT): Mr A is at high risk for opioid abuse.
- Implement a written opioid treatment agreement outlining the conditions under which you will prescribe opioid therapy.
- Request his past medical records to verify his verbal report.
- Prescribe hydrocodone/acetaminophen 5 mg/500 mg 2 q6h, 56 tablets for 1 week.

Five Days Later
- Mr A calls for an early refill. Hydrocodone is not helping his pain, but along with alcohol is the only thing that helps his anxiety and sleep.
- Medical records confirm his stated history.
- Ask him to come in for evaluation. Review the treatment agreement and the fact that he violated it, and obtain a urine sample.
- Your nurse arranges a referral to a psychiatrist in 2 weeks and a local pain specialist in 12 weeks.
- Prescribe 2 transdermal fentanyl patches 25 µg q72h with a follow-up visit in 6 days.
Interim Call
■ Mr A’s wife is worried about the patient lying around the house doing nothing.
■ You ask her to accompany Mr A on his visit that week.

Six Days Later
■ Mr A keeps his appointment but complains that his pain is out of control and that he needs more medication. The patches “don’t stay on.”
■ His wife reiterates that he lies around all day, is not bathing, and it appears to be because his pain is uncontrolled. She is eager for her husband to improve his function.
■ Prescribe SR morphine q24h 30 mg, 7 tablets.

Seven Days Later
■ The psychiatrist diagnoses Mr A as depressed and initiates fluoxetine. He is unable to make a determination about his pain or addiction.
■ Mr A comes in looking disheveled—he states that he lost his morphine the previous day.
■ His wife states that his function has not improved.
■ Another urine sample is sent to the laboratory for testing. The results 24 hours later reveal hydrocodone, marijuana, and morphine.

What Next?
■ Explain that because opioids are clearly not improving his function you will not continue to prescribe them, at least until his referral to the pain specialist in 10 weeks. Mr A is angry, but you reiterate that the opioid therapy is harmful to him.
■ Refer Mr A to a substance abuse specialist and prescribe clonidine to treat withdrawal.
■ You arrange for Mr A to attend a weekly physical rehabilitation program.
■ Further explain that you will see him every week to support him through this time. He agrees to come to the office the following week, and continues to do so.

Twelve Weeks Later
■ The pain physician tries an epidural steroid injection, with little success. No other evaluation or treatments were offered.
■ You refer the patient to a pain psychologist for weekly visits and continue to see him every 2 weeks.

Outcome
■ The pain psychologist recommends you initiate a regimen of SR morphine q24h 30 mg, 7 tablets weekly, to be doled out daily by Mr A’s wife.
■ The patient achieves some relief from this regimen and continues to work with the psychologist.

Conclusion
Chronic pain is a common presenting complaint in many practice settings and has substantial effects on patients’ QOL and ability to work. Opioid analgesics may be required to relieve moderate to severe pain and it is therefore important for physicians to identify when opioids might be useful, by careful patient assessment, selection, and monitoring, and to understand the principles of prescribing opioids. At the same time, it is just as essential that physicians are able to identify patients for whom opioid analgesia may create more harm than not using this treatment option. Physicians should be prepared to develop an “exit strategy” for such patients already being treated with opioids, and to formulate a plan to manage and support these patients with other pharmacologic and nonpharmacologic modalities.