Opioid Prescribing: Clinical Tools and Risk Management Strategies

Introduction

Approximately 70 million adults in the United States live with chronic pain (1), and in the primary care setting, chronic pain is prevalent in 5% to 33% of patients (2). The treatment of chronic pain is directed both at amelioration of the etiology for the pain, whenever possible, as well as administration of one or more pain relieving strategies **(Table 1)**. Achieving effective pain management is a complex task that draws on both the art and science of medical practice. Clinicians must get to know their patients well enough to understand the relationship between subjective complaints and the impact of pain on various functional outcomes.

Chronic pain is defined by the International Association for the Study of Pain (IASP) as pain that has persisted beyond 3 months, the normal tissue healing time (3). In patients whose original cause of nociception may have resolved, persistent pain appears to result from neuroplastic changes in either or both the peripheral and central nervous system (4).

Concomitant anxiety, depression, and insomnia are common conditions that exacerbate, and even amplify, pain. Similar outcomes occur with injuries or diseases affecting neural tissues (neuropathic pain) or when there is persistent pain due to ongoing nociceptive processes associated with chronic conditions (e.g., osteoarthritis). A growing chronic pain population includes patients who are in remission from, or cured of, cancer, and who are now suffering from intractable, painful conditions secondary to chemotherapy, radiation therapy, or surgery.

Opium and its derivatives have been used for thousands of years to relieve pain and suffering. More recently, their use in hospitalized patients with severe pain and in patients with advanced medical illness, such as cancer, has been supported by expert advice. Based on the successful use of opioids in cancer pain, treatment of chronic noncancer pain with opioids

Table 1. Categories of Pain Treatments

Category	Examples
Nonopioid drugs	Acetaminophen, nonsteroidal anti-inflammatory drugs
Adjuvant analgesics	Antidepressants, anticonvulsants
Opioids	Morphine, oxycodone, fentanyl, methadone, oxymorphone, hydromorphone
Rehabilitative approaches	Modalities (heat, cold, transcutaneous electrical nerve stimulation), physical therapy, occupational therapy
Psychological approaches	Cognitive behavioral therapy, specific techniques (biofeedback, hypnosis, relaxation), other psychotherapies
Injection therapies	Trigger point injections, joint injections, spinal injections
Neural blockade	Sympathetic nerve blocks, medial branch block, celiac plexus block
Implant therapies	Spinal cord stimulator, intrathecal pump
Surgical approaches	Cordotomy, neurectomy
Complementary and alternative medicine approaches	Acupuncture, chiropractic therapy, massage, nutritional approaches and nutraceuticals, energy therapies
Lifestyle changes	Weight loss, exercise

Adapted from: Fine PG, Portenoy RK. A clinical guide to opioid analgesia, 2nd edition. New York, NY: Vendome Group LLC; 2007.

Table 2. Barriers to Opioid Prescribing

Clinician Barriers
• Lack of education about opioids and current standards for pain management • Fear of toxicity • Fear of addiction • Fear of being "had" or "scammed" • Fear of regulatory agency scrutiny
Patient Barriers
• Fear of focusing on symptoms rather than cause • Belief that pain is inevitable • Fear of adverse effects • Fear of addiction

followed (5,6). However, an increase in the use of opioids for recreational purposes and a stricter regulatory climate has resulted in greater caution with their use. Since poor pain control and misuse/abuse of opioids can both lead to serious morbidity and mortality, clinicians need accurate information and guidance on the appropriate use of opioids as a component of chronic pain management, including risk assessment and management (7).

For optimal patient care, clinicians must have current knowledge of the pharmacology of opioid analgesics, including such characteristics as relative potency, pharmacokinetics, pharmacodynamics, formulation differences, and possible drug interactions. They must be able to differentiate among the disease of addiction and the pharmacobehavioral phenomena of physical dependence, tolerance, and pseudoaddiction. Finally, they must be able to recognize aberrant drug-related behaviors and formulate a differential diagnosis to identify, prevent, or treat medication misuse, abuse, and inadequate treatment (8).

Tools are available to evaluate patients as potential recipients of opioid therapy from a relative risk standpoint, but clinicians must also be confident in their ability to apply well-defined principles of prescribing and practice in order to maximize benefits and minimize risk. Clinicians may fear that prescribing opioids will inevitably lead to drug abuse or addiction. They may also believe that patients are faking or exaggerating their pain symptoms to obtain opioids. These beliefs have stigmatized the therapeutic use of opioids **(Table 2)**.

It should be emphasized that patients with chronic pain who receive long-term opioid therapy do not typically experience complete elimination of their pain (9). An effective pain regimen may provide satisfactory relief of the agonizing pain, and result in episodes of tolerable pain interspersed with pain-free periods, or residual, continuous but tolerable pain with or without breakthrough pain (BTP) episodes. However, the difference between a 9 and 5 on a pain rating scale, in which 10 represents "unbearable" pain, may be highly significant to many chronic pain patients and, among other functional outcomes, is often the goal in clinical practice.

Maximizing Outcomes with Appropriate Use of Opioids for Pain Management

Mechanism of Action

The primary site of action of most opioid analgesics is the mu-opioid receptor, which is expressed in the dorsal horn of the spine and in multiple regions in the brain (10). Research has shown that highly variable receptor activation and localization within the central nervous system are responsible for the range of responses seen among patients for the various opioid medications (11). Inter-individual differences also occur because of genetic polymorphisms that influence an individual's response to a particular opioid. For example, this can manifest as a decreased ability to metabolize the prodrug codeine to the active drug morphine in one patient compared to another. In addition, factors such as age and renal and hepatic function play a role in determining inter-individual variability in response to morphine (10).

Efficacy

An opioid trial is the only way a clinician can determine the efficacy and tolerability of a particular agent in a particular patient. There are published reports of opioid

Table 3. Short-acting Opioids

Combinations	Ingredients
Vicodin	Hydrocodone/acetaminophen
Percocet	Oxycodone/acetaminophen
Percodan	Oxycodone/aspirin
Tylenol #3	Acetaminophen/codeine

Single-entity drugs	Ingredient
MSIR	Morphine
Oxy IR	Oxycodone
Opana	Oxymorphone
Actiq	Fentanyl - transmucosal
Fentora	Fentanyl - transmucosal
Ultram	Tramadol
Nucynta	Tapentadol

efficacy in various pain-related conditions, but these are mostly short-term studies, and research is needed on the long-term effectiveness of opioid therapy (12). While the mu-agonist opioids used in clinical practice are not identical, the pharmacologic characteristics of these agents are less important in identifying an agent that will be effective in a given patient than are the variations in response of an individual patient to different medications (9).

Because a patient may have an inadequate response to one opioid but a satisfactory response to another, sequential opioid trials may be needed to identify the agent that yields the best efficacy and minimizes adverse effects (AEs), including nausea, sedation, and constipation. This is in part because of incomplete cross-tolerance among mu-opioid analgesics, which reflects their differing selectivity for mu-opioid receptor subtypes (13). By adjusting the dosing, the clinician can switch a patient from one opioid with a relatively high potency to another with a relatively lower potency, thereby regaining analgesia or reducing AEs, a process known as opioid rotation (14,15).

Opioid Selection

Because there is such variability between individuals in their response to particular opioids, the initial agent selected may not necessarily be the best option for long-term treatment. Several long-acting and short-acting opioid formulations are available to help tailor chronic pain management to the individual patient.

Short-acting opioids (SAOs), whose durations of action range from 2 to 4 hours, are often used during initial dose titration and in patients whose pain occurs for only a few periods during the day. They are available as single-entity medications or in combination with a nonopioid, such as acetaminophen or an NSAID **(Table 3)**. After titration is completed, the patient can be converted to an equivalent dose of a long-acting opioid (LAO), although some patients prefer to stay on the SAO for the control of continuous pain and BTP (16).

An LAO is recommended to control pain around the clock in patients with consistent pain levels. In general, LAOs are sustained-release formulations of a short-acting agent, thereby providing consistent and prolonged plasma drug levels with fewer peak and trough fluctuations **(Table 4)** (16). SAOs can be added as needed to the baseline regimen to control BTP and any pain that may occur with increased physical activity. To manage BTP, an SAO is generally given in a dose calculated to be 5% to 15% of the total daily opioid dose (9).

Rapid-onset opioids (ROOs), including oral transmucosal fentanyl citrate (as a lozenge on a stick), fentanyl buccal tablets, and the newly approved fentanyl soluble film, have been designed as rescue medication for sudden, severe pain flares that occur against a backdrop of well-controlled baseline pain in opioid-tolerant patients. These agents are approved for cancer-related BTP in opioid-tolerant patients. In studies of patients with noncancer BTP, these agents have demonstrated efficacy and safety, but their long-term effectiveness and potential for abuse are concerns (17). As with the decision to prescribe any opioid, prescribing an ROO should be based on adherence to principles of prescribing and practice, including risk assessment,

Table 4. Long-acting Opioids

Oral sustained-release	Formulation	Duration of effect
Morphine (Avinza, Kadian, MS Contin, Oramorph SR)	Oral CR, SR, ER	8 – 24 h
Morphine/naltrexone (Embeda)	Oral ER	8 – 24 h
Oxycodone (OxyContin, oxydone ER)	Oral CR, ER	8 – 12 h
Oxymorphone (Opana ER)	Oral ER	12 h
Tramadol (Ultram ER)	Oral ER	24 h
Transdermal		
Fentanyl (Duragesic, fentanyl generic)	TD	48 – 72 h
Long half-life		
Methadone (12 – 150 h)	Oral	6 – 8 h
Levorphanol (12 – 15 h)	Oral	3 – 6 h

Adapted from: Fine PG, Mahajan G, McPherson ML. Long-acting opioids and short-acting opioids: appropriate use in chronic pain management. *Pain Med.* 2009;10(S2):S79-S88.

benefit-to-risk evaluation, and consideration of all available therapies for the patient's pain (7).

Dosing for ROOs is calculated independently, as there is no correlation between the baseline dose and the rapid-onset dose. Frequent episodes of BTP may be an indication that baseline pain is being inadequately treated. In such instances, the baseline dose may need to be increased, along with similar increases of the ROO or SAO dose (18).

Table 5. Abuse-resistant and Abuse-deterrent Technologies

Chemical deterrence
• Block reward unless taken orally: NRP290 • Block reward/induce aversive effects if crushed/dissolved: Embeda, ELI-216
Physical abuse resistance
• Remoxy • OxyContin (new formulation)
Chemical deterrence and physical resistance
• Acurox
Reduce opioid adverse effects and block reward
• Oxytrex

Adapted from: Gershell L, Goater JJ. Making gains in pain. *Nature Rev Drug Discov.* 2006;5(11):889-890; Lavine G. Abuse deterrence focus of upcoming opioid formulations. *Am J Health Syst Pharm.* 2008;65(5):381,385; Webster LR, Butera PG, Moran LV, Wu N, Burns LH, Friedmann N. Oxytrex minimizes physical dependence while providing effective analgesia: a randomized controlled trial in low back pain. *J Pain.* 2006;7(12):937-946.

New Research

In response to the needs of patients and the clinicians who treat them, much of the new research in pain management has been focused on developing opioid formulations that might mitigate against abuse. Altering the delivery system of long-acting opioid formulations through physical means is one strategy for creating a tamper-resistant pill or capsule. A different method employs a pharmacologic approach, such as embedding the opioid antagonist naltrexone as a core within the active agent. When taken as directed, the opioid is absorbed with little or no absorption of the antagonist. However, manipulation of the compound, such as crushing, damaging, or dissolving the drug or mixing it with alcohol, is designed to cause the antagonist to be released at doses sufficient to blunt euphoric effects. A recently approved long-acting opioid combination of morphine and naltrexone (Embeda™, King Pharmaceuticals, Inc.) is an example of such technology for use in patients who require extended dosing and are opioid tolerant. Additional abuse-resistant and abuse-deterrent technologies are summarized in **Table 5**.

Table 6. Principles of Opioid Prescribing

Patient selection	**Perform comprehensive assessment** • Full characterization of pain complaint • Evaluation of relevant comorbidities • Current substance abuse • Personal history of substance abuse • Family history of substance abuse
Opioid selection	**Consider** • Severity and pattern of pain • Age, medical comorbidities, individual differences, previous opioid experiences • Drug-specific differences
Route selection	• Use least invasive route possible • Consider patient characteristics and adherence
Dosing	**Initiating therapy** • Consider previous dosing requirements and relative analgesic potencies • Start with lowest likely effective dose **Increasing dose** • Increase in increments (30% to 100%) • Size of increment and time interval between increments influenced by severity of pain and adverse effects • Increase dose until adequate analgesia occurs or dose-limiting adverse effects occur **Schedule** • Consider around-the-clock or as needed dosing depending on temporal pain patterns **Rescue** • Consider rescue medication for breakthrough pain
Monitoring	**Monitor** • Treatment efficacy and adverse effects • Aberrant behaviors, other responses over time **Follow-up** • Modify frequently and tailor to patient's clinical and social circumstances

Adapted from: Fine PG, Portenoy RK. A clinical guide to opioid analgesia, 2nd edition. New York, NY: Vendome Group LLC; 2007.

Tapentadol (Nucynta™, Pricara, Division of Ortho-McNeil-Janssen Pharmaceuticals, LLC) was approved in November 2008 and was the first new analgesic molecule in 25 years. It has dual mechanisms of action: mu-opioid agonism and norepinephrine reuptake inhibition. Phase 3 studies showed efficacy in patients that was equivalent to that of oxycodone, but with a significant reduction in typical opioid-related gastrointestinal AEs.

Prescribing Principles

The principles of opioid prescribing are summarized in **Table 6**. An important initial step in determining the suitability of opioids for a chronic pain patient is a comprehensive assessment, including a complete medical and psychological history, differential diagnosis of the presenting symptom(s), and analysis of relevant comorbid conditions (9). A discussion about personal or family history of opioid abuse can help predict the likelihood of future aberrant drug-taking behaviors. To help determine whether opioids are appropriate, the clinician must perform a risk-to-benefit analysis for the range of treatment options available, based on each individual patient's medical, psychological, and social circumstances. All individualized treatment plans should consider nonpharmacologic and nonopioid approaches (7).

The importance of individualized treatment cannot be overemphasized, as clinical trials are not designed to identify the best treatment regimen in a given situation to manage chronic pain. Few studies have directly compared LAOs and SAOs for chronic pain, and no strong data exist that demonstrate a benefit of one over the other in terms of analgesia, functionality, quality of life, or aberrant behaviors (19-22). Moreover, clinical trials are generally too short in duration to provide meaningful evidence to support long-term opioid therapy. While studies show that many patients respond well to opioid therapy, many patients in these studies discontinue therapy because of insufficient pain relief or intolerable AEs. In clinical practice, alternative approaches include opioid rotation, dose titration, and/or additional pharmacologic or nonpharmacologic therapies if the initial agent proves to be ineffective at meeting predefined therapeutic goals.

Initiation and Titration

When initiating an opioid trial in an opioid-naïve patient, the lowest likely effective dose of an SAO is generally preferred, because it can be titrated safely while observing for therapeutic effects and dose-limiting AEs. The dose should be increased incrementally, with size of the increment and interval between increments influenced by the degree of pain relief, functional improvements, and AEs experienced by the patient (9). A dose increment of 30% to 50% is generally safe and usually large enough to produce a change in analgesia. The dose should not be escalated until drug plasma levels have reached a steady state, which takes approximately 5 half-lives, or about 1 or 2 days for most of the SAOs currently available (9). If the pain is severe, and someone is home with the patient to monitor for and respond to serious AEs (e.g., excessive sedation, cognitive impairment, or respiratory depression [including new onset of snoring or apneic episodes while sleeping]), the dose may be increased by an increment of 100%. Alternatively, the amount of additional opioids needed to control BTP per day can be calculated and added into the fixed-schedule administration (9).

There is no predictable maximal therapeutic dose with single-entity opioid analgesics, but dose-limiting AEs do commonly occur (23). A goal of opioid therapy is to identify a dose that results in the greatest pain relief with the least amount of AEs. Doses of opioids marketed with a nonopioid analgesic are limited by the maximum dose of the nonopioid drug. For example, the limit for acetaminophen is 4 g/day in patients without compromised liver function, renal insufficiency, or history of alcoholism. After a stable dose is achieved with an SAO, it may be converted to an LAO to simplify patient adherence and provide continuous pain relief.

Some opioid formulations can be dangerous when initiating treatment and should not be used. For example, transdermal fentanyl has a higher drug concentration than opioid-naïve patients may be able to tolerate (24). Methadone has a long and variable half-life, metabolic instability relative to most other opioids, and requires additional time when making dosing adjustments. In addition, its complicated pharmacokinetic and pharmacodynamic properties and potential for *torsade de pointes* complicate its use, particularly when converting

Table 7. Clinical Reasons for Changing Opioids

Lack of efficacy
• Worsening of existing pain or underlying disease process • Development of opioid analgesic tolerance • Inability to tolerate effective dose • Dose required to produce analgesia exceeds APAP maximum daily dose recommendations (4 g/day) in patients on combination products (e.g., hydrocodone/APAP)
Development of intolerable AEs
• Gastrointestinal (i.e., constipation, nausea, vomiting) • CNS (i.e., sedation, somnolence, dysphoria, hallucinations, myoclonus) • Cardiovascular (i.e., orthostatic hypotension due to histamine release)
Change in patient status
• Inability to swallow • Poor peripheral vascular status/poor absorption of transdermal medications • Requirement of high-dose opioids not practically administered by oral, rectal, or transdermal routes
Practical considerations
• Availability in local pharmacies • Cost • Amount of opioid needed • Route of administration • Opiophobia (fear of one or more of the opioids, e.g., morphine that may be associated with death or addiction)

Adapted from: Gammaitoni AR, Fine P, Alvarez N, McPherson ML, Bergmark S. Clinical application of opioid equianalgesic data. *Clin J Pain.* 2003;19(5):286-297.

from another opioid. An initial electrocardiogram prior to administering methadone should be considered to identify any Q-T interval abnormalities, and ongoing monitoring is recommended in patients with known heart disease (9).

Opioid Rotation

Opioids have no known dosing ceiling to control pain, and there are clinical reports of very high doses in a small set of patients (25,26). There is wide variation in the dose required to achieve maximal comfort and function without producing sedation or physical impairment, and some patients may require morphine or its equivalents in doses over 1000 mg/day for chronic pain (27). However, the clinician should consider rotation to another opioid when the patient's current medication is no longer effective; AEs become unacceptable; or the dose needed for pain relief requires too many daily units to maintain conveniently **(Table 7)** (14,15,28,29).

Opioid rotation, a planned switch from one opioid to another in an effort to improve outcomes, is a commonly used strategy for achieving a favorable balance between analgesia and AEs. The potency, efficacy, and AEs of different opioids can vary unpredictably within an individual and among different patients; patients often show incomplete cross-tolerance when rotated from one opioid to another. For a successful outcome, the clinician must be prepared to devote the time needed to the titration process, and to make adjustments to therapy as required.

When considering opioid rotation, the clinician should perform a complete reassessment of the pain and its treatment that includes checking the patient's total daily dosage and considering if adding a co-analgesic would be helpful. The clinician must take into account the relative potency or dose ratio required to produce an equivalent degree of analgesia.

Equianalgesia refers to the relative doses of 2 agents that provide approximately equal pain relief (28). Several equianalgesic tables exist, but they should be interpreted with caution because typically they are based on single-dose studies using opioid-naïve subjects, which is generally not reflective of a clinical pain practice (15,29). This caution should be particularly heeded when converting from an initial opioid to methadone (30). A recent expert panel convened to establish best practices proposed a guideline that incorporates the principles of the equianalgesic dose table while adding elements to promote increased safety during opioid rotation (14).

Managing AEs and Comorbidities

The effective management of opioid-related AEs increases the likelihood of a favorable outcome, including the potential for dose escalation to control pain. The most common and persistent AE is bowel dysmotility, which can lead to constipation and rarely to obstipation and bowel obstruction. The relationship of constipation and opioid use is usually clear, but further evaluation may

be warranted when another cause is suspected or the condition worsens for no apparent reason (9). Additional constipating agents (e.g., anticholinergic drugs or calcium supplements) must be considered as their effects will be additive, and taking action just on the opioid may be inadequate to fully treat the constipation, and may significantly limit analgesia. A stepwise approach for managing opioid-induced constipation is presented in **Table 8**.

Other common AEs include nausea and vomiting, somnolence, cognitive effects, pruritus, sweating, dry mouth, and weakness. With the exception of bowel dysfunction, tolerance usually develops to somnolence and the cognitive effects of opioid therapy. Nausea should be promptly treated to prevent the development of a conditioned response to the opioid, which could complicate treatment and lead to a poor therapeutic response (9). Somnolence and cognitive impairment that does not resolve over several weeks should be investigated further to rule out other etiologies. If the relationship to opioid use is clear, reducing the dose or switching to another agent may resolve the condition. Treatment with a psychostimulant may be tried with careful monitoring for AEs. In older patients and those with early dementia, donepezil has been shown to be effective for short-term relief of opioid-related sedation (31).

Exit Strategies

When ample trials of opioids prove ineffective at meeting therapeutic goals, or problematic use patterns prevail, the clinician may decide to discontinue opioid therapy. Withdrawal symptoms can be avoided by implementing a slow tapering schedule. Gourlay and Heit (32) have recommended reducing the dose of the opioid by 10% every 1 to 2 weeks until the patient reaches the bottom third, after which the dose is reduced by 5% every 2 to 4 weeks until complete. An exit strategy that has been mutually agreed upon by all parties prior to initiating opioid therapy is recommended. Such preparation may include distributing patient education materials that are attached to a patient-prescriber agreement.

Reaching this decision jointly with the patient is ideal, but if the patient decides to continue on opioid therapy with another clinician, it is reasonable to maintain the patient on his or her current dose for 30 days. Opioids may not be an optimal or appropriate choice for some patients for a variety of reasons, and even the vast majority of those who have demonstrated aberrant behaviors with opioids deserve other nonopioid analgesic options. If criminal behavior is discovered (e.g., altering prescriptions or selling drugs), the physician-patient relationship may have been sufficiently breached to justify discharging the patient from one's practice after referral to a substance abuse treatment program (32). Discharging a patient from one's practice is a severe step that is only warranted under rare circumstances. However, even in most cases where opioid discontinuation is appropriate or where there have been violations in a previously established written agreement, there are usually other options that can be tried short of termination from care.

Table 8. Stepwise Approach for Managing Opioid-Induced Constipation

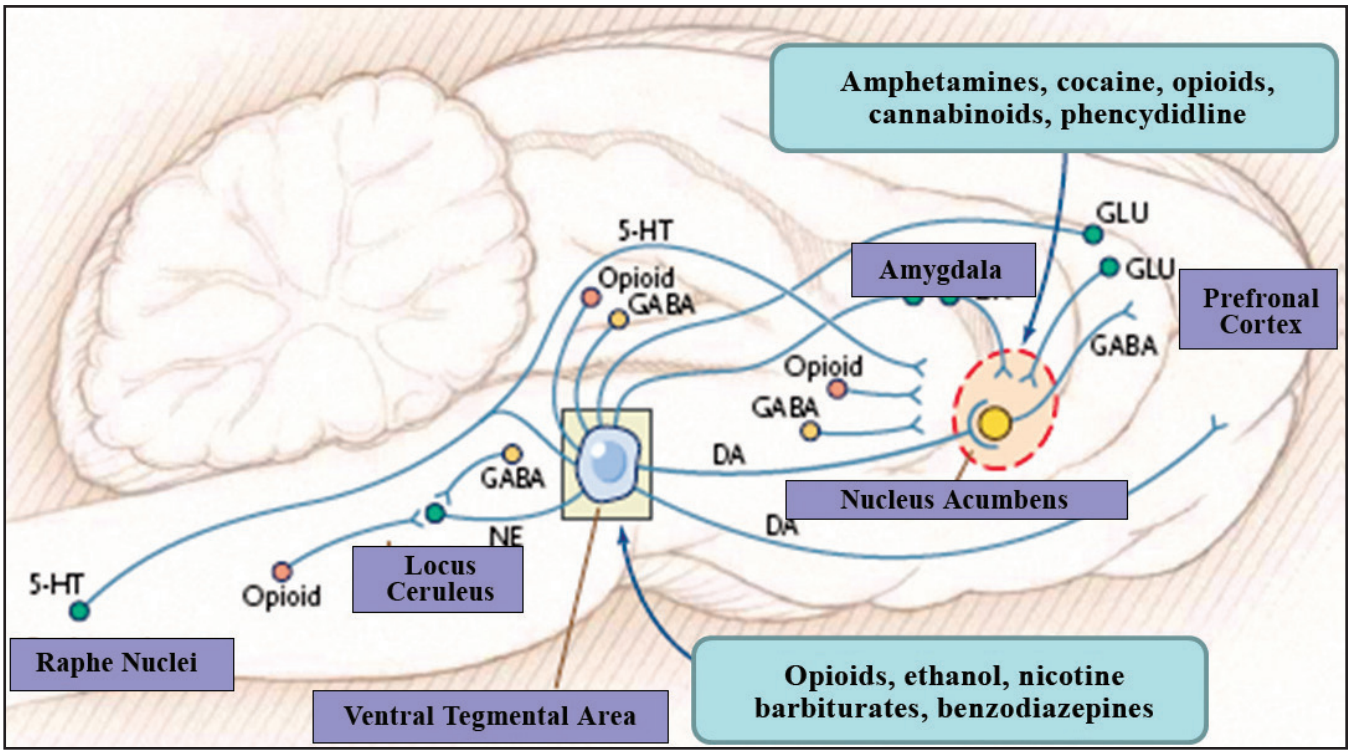
1. Nonpharmacologic approaches for all patients
• Increase fluid intake as tolerated • Increase dietary fiber as tolerated (unless patient is severely debilitated or bowel obstruction is suspected) • Encourage mobility and ambulation if appropriate • Ensure comfort and privacy for defecation • Encourage bowel movements at the same time each day • Rule out or treat impaction
2. Consider pharmacologic interventions and discuss approaches with the patient
• Intermittent use (every 2 to 3 days) of an osmotic laxative, such as magnesium hydroxide, magnesium citrate, or sodium phosphate • Trial of a daily softening agent (e.g., sodium docusate) alone • Intermittent use (every 2 to 3 days) of a contact cathartic, such as senna or bisacodyl • Daily use of a contact cathartic preparation (with or without a concurrent softening agent) • Daily use of lactulose or sorbitol • Daily use of polyethylene glycol
3. Adjust dose and dosing schedule of selected therapy to optimize effects
4. Switch or combine conventional approaches if initial therapy is inadequate

Adapted from: Fine PG, Portenoy RK. A clinical guide to opioid analgesia, 2nd edition. New York, NY: Vendome Group LLC; 2007.

Misconceptions regarding the nature of addiction have historically been barriers to effective chronic pain treatment with opioids. The current public health crisis of prescription drug abuse is real and must be a concern for all opioid prescribers. However, such consideration will only be effective if based upon accurate data and understanding of abuse, misuse, addiction, and appropriate outcomes of analgesia. Misunderstanding these vital elements of responsible opioid prescribing has resulted in opioids being associated with fear of abuse and addiction to a point of limiting their appropriate use for pain patients (7). Until recently, physical dependence and tolerance were equated with addiction, and withdrawal was considered a critical indicator of addiction. However, this construct does not explain high rates of relapse long after withdrawal, or the observation that addiction is rare in patients who become physiologically dependent on opioids while using them for pain control. Increasing understanding of the scientific basis of addiction demonstrates that the disease is driven by reward phenomena rather than by physical or psychological dependence (33,34).

The reinforcing effects of all drugs of abuse are mediated by dopamine stimulation in the mesolimbic system of the brain **(Figure 1)** (35). This response is not influenced by habituation, and each dose of the drug stimulates the release of dopamine. Dopamine, in turn, promotes associative learning about the drug and anticipation of its rewarding effects. The amount and speed at which dopamine is exposed to the reward center of the brain is

Figure 1. Common Reward Pathway: Mesocorticolimbic Dopamine System



5-HT = serotonin; GABA = gamma-aminobutyric acid; NE = norepinephrine; DA = dopamine; GLU = glutamine.

Animal models have been used extensively to study mechanisms of addiction. This figure illustrates common reward pathways as shown in the rat brain. The neuronal pathways of drug addiction are components of the mesocorticolimbic dopamine systems that originate in neurons in the ventral tegmental area. Projections from these neurons to the limbic structures, such as the nucleus accumbens, amygdala, and hippocampus form the mesolimbic circuit, which is responsible for conditioned responses linked to craving as well as the emotional and motivational changes of the withdrawal syndrome. Projections from the ventral tegmental area to the prefrontal cortex, orbitofrontal cortex, and anterior cingulate make up the mesocortical dopamine circuit, which accounts for the conscious experience of the effects of drugs, drug craving, and the compulsion to take drugs. All drugs of abuse act on this system at different levels.

Camí J, Farré M. Drug addiction. *N Engl J Med.* 2003;349(10):975-986.

a function of the pharmacokinetics of the drug and the manner of its use (4). The greater the amount of dopamine and the more rapid its release, the more likely is the drug-induced reward. Drugs that produce rapid peaks, such as the highly lipophilic opioids (e.g., diacetylmorphine [heroin] and fentanyl) are thought to generate cravings and compulsive use in susceptible individuals. Slower-release compounds and the more hydrophilic agents (e.g., morphine) do not provide the same "spike," and are, therefore, thought to be less potentially addicting (35).

Tolerance, Dependence, and Addiction

In 1999, the American Pain Society (APS), the American Academy of Pain Medicine (AAPM), and the American Society of Addiction Medicine (ASAM) established a set of definitions that would promote the use of conceptually consistent language by clinicians, regulators, and the public to improve the care of people with pain and with addictive disorders. These definitions embody current clinical and scientific understanding **(Table 9)** (36). In addition to tolerance, dependence, and addiction, the more recently invoked term, pseudoaddiction, has been defined by Weissman and Haddox (37) as the need to seek additional medications due to the undertreatment of pain. When pain is treated appropriately, aggressive drug-seeking behavior ceases.

Understanding these definitions can help clinicians distinguish physical dependence and tolerance, which are neuropharmacologic phenomena, from addiction, which is a behavioral as well as a neuropharmacologic phenomenon. The behavioral characteristics incorporated into the definition of addiction can help distinguish it from other forms of aberrant drug use. For example, some individuals self-medicate with a variety of substances, including opioids, to cope with stress, relieve anxiety, or aid sleep. Others use opioids to get high, but do not use them in the compulsive way indicative of addiction. Some may divert their medications to sell them for profit or give them to others who are also in pain. With careful evaluation of the patterns and purposes of a patient's aberrant drug use, the clinician can determine an appropriate clinical response (36).

Differentiating Aberrant Behaviors

It is nearly impossible for clinicians to determine who is at risk for addiction, because there is no definite test or physical sign that can predict the successful use of opioids for pain control (38). Aberrant behaviors related to abuse or addiction have been described and can be placed on a continuum that ranges from nonexistent to egregious (39). Despite a lack of consensus on how to interpret these behaviors, most physicians find such activities as unscheduled visits, multiple telephone calls to the clinic, unsanctioned dose escalations, obtaining opioids from more than one source, selling prescription drugs, and forging prescriptions as indicative of abuse (40,41).

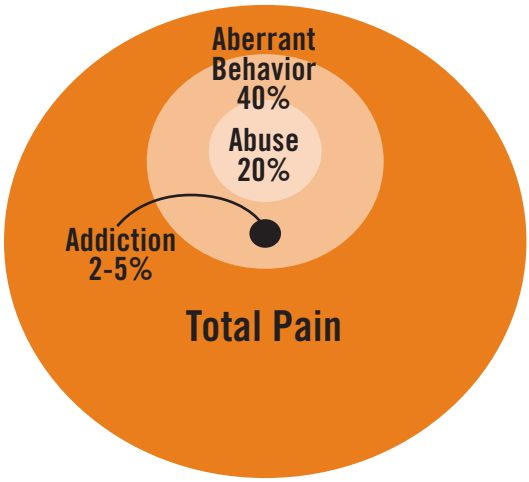
However, behaviors that suggest abuse may only reflect a patient's attempt to feel normal and stem from wanting to treat depression or anxiety or from having pain that is undertreated (39). **Figure 2** illustrates the relationships between aberrant behavior, abuse, and addiction in patients being treated in a pain clinic (39). The prevalence

Table 9. Definitions developed by the American Academy of Pain Medicine (AAPM), the American Pain Society (APS), and the American Society of Addiction Medicine (ASAM)

Term	Definition
Addiction	Addiction is 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	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, decreasing blood level of the drug, and/or administration of an antagonist.
Tolerance	Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more or the drug's effects over time.

Adapted from: American Academy of Pain Medicine, American Pain Society, and American Society of Addiction Medicine. Definitions related to the use of opioids for the treatment of pain. http://www.painmed.org/pdf/definition.pdf. Approved February 2001. Accessed December 2, 2009.

Figure 2. Aberrant Behavior, Abuse, and Addiction in a Pain Clinic



Adapted from: Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the Opioid Risk Tool. *Pain Med.* 2005;6(6):432-442.

of addiction (2% to 5%) is a subset of the percentage of those exhibiting abuse (20%), and this group is a subset of those exhibiting aberrant behavior (40%). The ability to determine when a patient's aberrant behavior becomes abuse requires the clinician's knowledge and judgment. Certain characteristics of aberrant behaviors, however, should clearly point to a problem with managing opioid intake. For example, a patient exhibiting multiple, egregious behaviors that persist, despite repeated warnings and that require significant time and resources to manage, is likely to have a problem with abuse and possibly addiction (4).

For successful treatment of pain with opioids, any aberrant drug-related behavior must be monitored, documented, and addressed (4). The first diagnosis to consider is that of uncontrolled pain. The presence of mental disease, family stress, and other underlying factors may best be evaluated during a psychiatric or behavioral consultation.

Establishing definitions is an important aspect of documentation. Recreational use or criminal intent is also part of the differential diagnosis, as is, of course, addiction. Pseudoaddiction, characterized by drug-seeking behavior that resembles addiction, should, in theory, resolve when the pain is adequately controlled. A patient who is a "chemical coper," and misuses or abuses medication in the pursuit of reducing psychological stress or other symptoms, should be referred for appropriate treatment of the underlying disorder. Someone who engages in "rational" misuse by escalating his or her own doses with the intent of obtaining better pain control requires education and intensive monitoring and treatment. Patients with chronic pain, a history of substance abuse, and an underlying psychiatric disease should be treated for all 3 conditions simultaneously for optimal benefit. A patient with the disease of addiction requires treatment for the addiction as well as for the chronic pain. Balancing risk and benefits of potential treatments must be of paramount concern and, if possible, such patients should usually be referred to an addiction specialist.

Aberrant behaviors generally go unnoticed by the clinician and are either reported by the office staff, the patient, the patient's family, or the pharmacy. Reports of aberrant behavior may also be obtained from a prescription monitoring database, drug screening, or police report. The clinician can often receive valuable insight into the patient's circumstances by maintaining a willingness to listen and a caring attitude. In general, a compliant patient with well-controlled pain and improvements in function and quality of life exhibits little or no aberrant behavior. At the opposite end of the spectrum, an addicted patient engages in egregious behaviors and experiences diminished function and quality of life after inappropriate drug use. Patients engaging in moderate aberrant behaviors may pose particular challenges, but if the clinician reacts therapeutically and proceeds with caution, these patients can often continue opioid therapy with success.

Risk Factors for Addiction

The likelihood of addiction developing in a chronic pain patient being treated with opioids is the result of a complex interaction between the properties of the drugs and the person at risk (8). Several factors have been identified that predict whether a patient is likely to display aberrant behavior consistent with abuse, including a personal or family history of substance abuse, a history of sexual abuse, and the presence of certain mental diseases (39). An individual's risk for drug abuse is also determined by his or her history, current life situation, and such factors as stress, presence of an abuse-prone environment, ingestion of a drug with binge potential,

Table 10. The 10 Steps of Universal Precautions in Pain Medicine

1	Make a diagnosis with appropriate differential	• Identify treatable causes for pain and direct therapy to the pain generator • In the absence of specific findings, treat symptoms • Address comorbid conditions, including substance abuse and psychiatric disorders
2	Psychological assessment including risk of addictive disorders	• Inquiry into personal and family history of substance abuse should not diminish a patient's complaint of pain • Perform patient-centered urine drug testing
3	Informed consent	• Discuss the proposed treatment plan including benefits, risks, and tolerance, dependence, and addiction at the patient's level of understanding
4	Treatment agreement	• Expectations and obligations of patient and clinician should be understood • Agreement plus consent forms the basis of the therapeutic trial
5	Pre- and post-intervention assessment of pain level and function	• Used to assess the success of medication and support continuation of therapy
6	Appropriate trial of opioid therapy with or without adjunctive medication	• Pharmacologic regimens should be individualized and based on clinical findings
7	Reassessment of pain score and level of function	• Regular assessment documents rationale to continue or modify treatment
8	Regularly assess the "Four A's" of pain medicine	• Analgesia, activity, adverse effects, and aberrant behavior
9	Periodically review pain diagnosis and comorbid conditions, including addictive disorders	• Treatment for each condition must be coordinated for positive outcomes
10	Documentation	• Complete recording of the initial evaluation and follow-up sessions, combined with an appropriate physician/patient relationship, reduces medicolegal exposure and risk of regulatory sanction

Adapted from: Gourlay DL, Heit HA, Almahrezi A. Universal precautions in pain medicine: a rational approach to the treatment of chronic pain. *Pain Med.* 2005;6(2):107-112.

and genetic predisposition. The more risk factors that are present, the greater the individual's risk of abuse (39).

Patient Selection

Opioid therapy is one of many options for managing chronic pain and can provide relief that has been elusive with other treatments. However, some patients seek treatment with opioids when, in fact, they are at high risk for poor outcomes because they suffer from an underlying drug abuse problem. Identifying these patients and guiding them to appropriate care is critical for managing risk for both the patient and prescriber.

Methods for Assessing Risk

Whenever the decision is made to initiate an opioid trial for long-term therapy, the treatment must include strategies for minimizing the risk of abuse. Creating an individualized treatment plan and providing an appropriate level of monitoring should be part of the care plan for all patients. Applying the same assessment of a patient's risk for drug abuse to all patients with chronic pain can improve patient care, reduce stigma, and minimize overall risk (38). The concept of "universal precautions" in the assessment and management of chronic pain patients is based on the same principles used in infectious disease: just as any patient requiring a blood draw for a simple lab test could have HIV, any pain patient could have a drug abuse problem. **Table 10** outlines the 10 steps of universal precautions in pain medicine.

Table 11. Opioid Risk Tool (ORT)

Item	Mark each box that applies	Item score if female	Item score if male
1. Family history of substance abuse			
• Alcohol	[ ]	1	3
• Illegal drugs	[ ]	2	3
• Prescription drugs	[ ]	4	4
2. Personal history of substance abuse			
• Alcohol	[ ]	3	3
• Illegal drugs	[ ]	4	4
• Prescription drugs	[ ]	5	5
3. Age (mark box if 16 to 45)	[ ]	1	1
4. History of preadolescent sexual abuse	[ ]	3	0
5. Psychological disease			
• Attention deficit disorder, obsessive compulsive disorder, bipolar, schizophrenia	[ ]	2	2
• Depression	[ ]	1	1
Total			
Total score risk category: low risk (0-3); moderate risk (4-7); high risk (≥8)			

Adapted from: Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the Opioid Risk Tool. *Pain Med.* 2005;6(6):432-442.

Estimating a patient's risk level for opioid abuse before initiating treatment can help the clinician establish an appropriate level of monitoring, and form the basis for consultation or referral. Patients generally fall into low-, moderate-, or high-risk potential categories for drug abuse. Categorizing patients this way is not intended to stigmatize high-risk patients, or deny them treatment for pain or other comorbid disorders; rather, such stratification should increase the likelihood of a good clinical outcome for all patients (4).

Screening Tools

Several screening tools are designed to assess risk of aberrant drug-related behavior in chronic pain patients, and are suitable for use in the primary care setting. The CAGE was an early scale for alcohol abuse that was later adapted to include drugs as the CAGE-AID (42), which includes the following questions:

In the past have you ever:

- Tried to **C**ut down or **c**hange your pattern of drinking or drug abuse?
- Been **A**nnoyed or **A**ngry by others' concern about your drinking or drug use?
- Felt **G**uilty about the consequences of your drinking or drug use?
- Had a drink or used a drug in the morning (**E**ye-opener) to decrease hangover or withdrawal symptoms?

Another brief tool that has been validated in the clinical setting is the Opioid Risk Tool (ORT), which consists of 5 questions that predict the probability of aberrant behaviors when prescribed opioids for pain **(Table 11)** (39).

The Screener and Opioid Assessment for Patients with Pain (SOAPP) is another validated, self-administered tool designed to evaluate the abuse risk in patients who are being considered for long-term opioid therapy (43).

Ensuring Patient Compliance

Ongoing monitoring for pain and aberrant drug-related behaviors is an essential aspect of opioid therapy and should be conducted as often as the patient's risk profile and treatment plan dictate. The most relevant areas for monitoring have been termed the "4 A's," and include analgesia, activities, adverse effects, and aberrant behaviors (44). Analgesia can be monitored with a pain intensity scale, both at baseline and at all subsequent visits. Activities are assessed by physical functioning, mood, family relationships, sleep pattern, occupational functioning, and overall functioning. Adverse effects include patient reports of tolerability of treatment-related AEs. Aberrant drug-related behaviors suggestive of drug abuse must be discussed with the patient and resolved. Isolated instances of aberrant behavior can often be attributed to unrelieved pain and managed. However, even relatively benign behaviors can indicate a problem if they occur more frequently than existing evidence indicates is within normal limits. For example, requests for early refills occurring more than 3 times within a 6-month period reflect greater difficulty in treatment compliance than what would be expected for 85% of patients (45).

Long-term management of opioid therapy is unique in each individual patient and is continually subject to adjustment. Changes in therapy may be needed because of a change in the patient's circumstances, discovery of new pain pathology, occurrence of a drug interaction or AE, or development of analgesic tolerance (38). Management of poorly responsive pain may require more aggressive treatment, rotation to an opioid with a more favorable benefit to risk balance, or addition of nonpharmacologic and pharmacologic measures (9). In some instances, the patient's pain may not respond to opioid treatment and an exit strategy must be initiated.

Adjustments may also be made to accommodate long-term treatment goals, such as switching from a short-acting to a long-acting opioid or switching to an alternative route of administration. At all stages of opioid-based pain management, assessment of aberrant behavior and risk of opioid misuse must be monitored and documented.

Risk Management for Clinicians

Despite wanting to treat chronic pain patients, clinicians may fear that the risk management issues surrounding opioid analgesics may be too difficult to manage. However, most of the measures that fall under the category of risk management constitute basic principles of good medical practice (7). Clinicians who prescribe opioids for chronic pain are obligated to implement therapy according to accepted principles of prescribing and to minimize the risk of misuse, abuse, addiction, and diversion through individualized application of risk assessment and management strategies. Each state works with the federal government to oversee the movement of controlled prescription drugs and minimize abuse and diversion. Historically, regulations that govern the use of controlled substances have emphasized enforcement and not patient care.

Recently, however, many states have attempted to address the need to protect clinical practice while reducing opioid abuse. The Federation of State Medical Boards has drafted a model policy for the medical use of controlled substances, which have now been adopted by most states (46). This model policy is used by state boards to judge the appropriateness of therapy, and should be considered as the basic approach to structuring and documenting opioid therapy (9). Other recommendations have been made by professional societies that are consistent with the risk

management principles outlined by the Federation (47,48). **Table 12** contains the key elements in the Model Policy for the Use of Controlled Substances for the Treatment of Pain and recommendations for their implementation in clinical practice.

Case Study

Ben is a 40-year-old heavy machine operator involved in Interstate Highway bridge refurbishing. He began experiencing recurrent low back pain in his early 20s after years of playing contact sports. He has had multiple acute severe pain episodes, and most recently tripped while descending from the cab of a truck, resulting in "a sharp pain in my lower back that brought me to my knees." A friend brought him home that day and Ben treated his back pain with acetaminophen and application of ice packs. After unsuccessfully trying to "work through the pain," he made an appointment with his doctor. During the visit, Ben rates his pain as 9 on a scale of 0 (no pain) to 10 (worst pain imaginable), and describes the pain as a continuous sharp ache in his lower back that radiates down his right buttock and thigh. With certain bending, lifting, sneezing/coughing, or twisting movements (e.g., while "toileting"), the pain travels to his right foot. Over-the-counter acetaminophen 1000 mg 4 times daily has not helped, and ibuprofen 800 mg "only takes the edge off." Only lying down on his side with a pillow between his legs reduces his pain levels. Ben is having trouble sleeping but denies being depressed—only frustrated at his situation. Past history is noteworthy for heavy alcohol use; he is not in a recovery program, but he states that he discontinued all alcohol use when he began his current job 2 years ago.

Physical examination reveals a positive straight-leg-raise test beyond 30 degrees on the right and an atelic gait with splinting. No sensory loss, weakness, or deep tendon reflex abnormalities in the right leg or foot are evident. There is palpable spasm in par spinal muscles, but no trigger points that reproduce radicular symptoms.

Findings are consistent with radiculopathic low back pain possibly due to L5/S1 disc herniation. Based upon the absence of "red flags" (e.g., localized bony tenderness, deformity, neurological loss, fever, malignancy), there is no indication for neuroimaging (49). Reassurance is provided along with counseling about signs and symptoms to monitor, for which urgent care should be sought. Ben is instructed to take ibuprofen 800 mg with meals, 3 times a day. He is provided with a prescription for tapentadol 50 mg up to every 6 hours for a maximum of 5 days. In addition, Ben is advised to remain active and use a heating pad or ice packs when his pain flares up. Ben is referred to a physical therapist for instruction about home-based stretching and core strengthening exercises.

At a one-month follow-up appointment, Ben reports little change in his pain, which occasionally causes him to miss work. He expresses concern for his family, as he is the sole income earner for his wife and 2 young children. He states that this episode differs from his previous back pain incidents because it is more persistent and intensely painful with "burning" down his leg into the inside and sole of his foot. Due to persistent radicular symptoms and re-examination that reveals reduced ankle jerk on the affected side, lumbar MRI is performed which confirms a L5/S1 disc herniation as well as a bulging disc at L4/L5.

Ben's doctor describes the potential benefits and risks of various treatment options for this condition, including epidural steroid injections and lumbar discectomy. He explains that clinical studies have alternately supported and refuted the efficacy of epidural steroid injections in the treatment of back pain, and although they benefit some patients with radicular pain, improvements are often limited in duration (50-52).

Ben states that he does not want to undergo surgery if it can be avoided, but he would like to pursue injection therapy if there is even a small chance he'll get some pain relief. He is referred to a pain specialist for a fluoroscopically guided, transforaminal epidural injection of local anesthetic and corticosteroid.

One month later, Ben returns to his pain specialist for a follow-up appointment, stating that the epidural steroid injection reduced his pain from 9/10 to 3/10 for approximately 2 weeks. Thereafter, the pain returned and is now as intense as it was on his first visit. He again expresses concern about being unable to work and provide for his family. He also mentions that he has

Table 12. Implementing the Model Policy for the Use of Controlled Substances for the Treatment of Pain

Guideline	Criteria	How to Integrate into Practice
Patient evaluation	• Document history and physical examination • Document pain history, comorbidities, history of substance abuse, and indication for opioid	• Make time to listen carefully to patients in pain using a reflective listening approach • Remain mindful of the need for suspicion without a rush to judgment • Look for signs of abuse, but recognize the complexities of presentation and the possibilities of pseudoaddiction • Remember that not treating pain is often not a "safe" option
Treatment plan	• State objectives that determine success (pain relief, improved physical and psychosocial function) • Adjust treatment over time to reflect individual patient needs • Prescribe nonopioid therapies when needed	• Use a function-based paradigm at diagnosis and for treatment plan • Develop list of functional losses and gains to be impacted by care, then track and modify • "Feeling better" without improved function may not reflect quality of life improvement • Modest pain score reductions may reflect significant gains in function
Informed consent and agreement for treatment	• Discuss risks and benefits of controlled substance with patient and/or family/guardian • Use one physician and pharmacy whenever possible • Consider written agreement if risk of abuse is high, including drug screening when requested, number and frequency of all prescription refills, and reason for discontinuing drug therapy (violation of agreement)	• Patients must fully understand potential risks and benefits of any procedure or treatment to be fully informed • Incorporate risk education information into a clear and transparent process, whether or not you are prescribing a controlled substance • Prepare educational materials and develop a process for implementation in advance • Use a written agreement/informed consent process to address key points
Periodic review	• Evaluate progress toward treatment objectives to determine continuation or modification of therapy • Satisfactory response includes decreased pain, increased function, and improved quality of life • Use objective indicators as well as information from family members and other caregivers • Reconsider or change treatment if progress is unsatisfactory	• Closely monitor treatment outcomes and be alert to wide range of adverse effects • Have means of measuring progress toward functional goals and clearly document • Patients bear the responsibility of attaining treatment goals and providing evidence • Assess functional goals and adjust as needed
Consultation	• Be willing to refer patients at particular risk for or misuse, abuse, or diversion • Consider consulting an expert for patients with history of substance abuse or comorbid psychiatric disorder	• Build a network of clinical experts to whom you can turn for specialized needs • Be clear with yourself about your expertise and don't hesitate to refer patients early • Remember that the most "difficult" patients may be the ones who need your help the most
Documentation	• Accurate and complete medical records should include: o Medical history and physical exam o Diagnostic, therapeutic, and laboratory results o Evaluations and consultations o Treatment objectives o Discussion of risks and benefits o Informed consent o Treatments o Medications (date, type, dosage, and quantity prescribed) o Instructions and agreements o Periodic reviews	• Documentation is essential at every step of pain care delivery • Document assessments, treatment agreements, education, action plans, and patient monitoring activities • Be clear and transparent about risk management decision making • Include specific information that can be understood by others reading the record
Compliance with controlled substances laws and regulations	• Physician must be licensed in the state and comply with applicable federal and state regulations	• Know regulations on controlled substances issued by state medical board and adhere strictly to them • Know and adhere to federal regulations issued in the Physicians Manual of the US Drug Enforcement Administration

Adapted from: Fine PG, Portenoy RK. A clinical guide to opioid analgesia, 2nd edition. New York, NY: Vendome Group LLC; 2007; Fishman S. Responsible opioid prescribing: a physician's guide. Washington, DC: Waterford Life Sciences; 2007.

developed a "short temper" that he attributes to pain-related stress, which is taking a toll on his relationship with his wife. He is struggling not to use alcohol to reduce pain and stress.

The pain specialist decides to initiate treatment with nortriptyline 25 mg at bedtime based on positive results from randomized controlled trials of tricyclic antidepressants for low back pain. This dose is slowly increased to 75 mg at bedtime during the next month. She also recommends various complementary and alternative medicine practitioners in the area who can help incorporate nonpharmacologic modalities into Ben's treatment plan.

One month later at his regularly scheduled follow-up visit, Ben reports that he has benefited from the nortriptyline without excessive daytime sedation or problems urinating. He also has been receiving weekly treatment from a certified acupuncturist. Ben's pain has been reduced from 9/10 to 5/10 throughout the day and he has returned to full-time work. Despite these improvements, he is occasionally forced to take extended breaks at work and often experiences sudden spikes of moderate-to-severe pain during the second half of his workday.

Ben's primary care physician (PCP) and pain specialist, who are working together to manage Ben's pain, both feel that he may benefit from an opioid in addition to nortriptyline. Before an opioid is prescribed, the PCP has Ben complete the Opioid Risk Tool (ORT) to assess potential risk of opioid abuse. Ben acknowledges that he used to smoke marijuana regularly when he was drinking, although he quit more than 2 years ago. Ben scores 5 on the ORT, placing him in the moderate risk category. The PCP reviews a written treatment agreement with Ben, both to document informed consent and structure a discussion within which he and Ben affirm their respective expectations.

Because of Ben's moderate risk level, his PCP includes unannounced urine drug testing (UDT) and pill counts in the care plan. A check of the state prescription monitoring program (PMP) ensures that Ben is not receiving opioids or other controlled substances from any other doctors. Strong admonition against concurrent use of alcohol or other sedating agents (e.g., "sleep aids") is given.

Ben's PCP prescribes morphine sulfate immediate-release (IR) 15 mg as needed up to 4 times daily in addition to nortriptyline 75 mg daily, and senna and docusate in anticipation of opioid and tricyclic-related bowel dysfunction. One week later, Ben reports that he is taking 4 morphine sulfate IR tablets daily, which has reduced his pain levels to 3/10, but he is constipated and uncomfortable, despite the laxation regimen.

The PCP decides to rotate Ben from morphine to oxycodone with the hope of reducing the AEs while maintaining the analgesia obtained with the opioid. Since Ben is taking a relatively low daily opioid dose and is not medically frail, a dose of oxycodone extended-release (20 mg every 12 hours), approximately equivalent to the total 24 hour dose of morphine IR (60 mg), is prescribed. Ben returns for a follow-up appointment and reports that the bowel regimen is now effective and his pain is generally under control, although there are times at work when his pain worsens after activities that put strain on his back.

The PCP conducts an independent, comprehensive assessment of the pain episodes, beginning with an in-depth evaluation of the pain character and temporal profile, and identification of potentially correctable causes. The assessment includes questions about the intensity, duration, and frequency of the episodes. In addition, inquiry is made into potential precipitants, functional impact, and what he does to obtain relief. Ben reports that he usually experiences 2 of these approximately hour-long episodes each day and that they almost always follow a lifting activity at work. Based on Ben's generally controlled baseline pain and his description of the episodes, the PCP determines that Ben is experiencing predictable, precipitated ("incident") BTP.

The PCP again reviews the potential benefits and risks of various treatment options. He considers modifying the baseline opioid regimen, but determines that an increased baseline opioid dose is not needed for most of the day and may lead to excessive opioid-related AEs. Again, Ben is adamant about not pursuing surgery, so his physician recommends applying a topical anesthetic patch (i.e., 5% lidocaine patch) before work each day. He also encourages continued adherence to the therapeutic stretching and core strengthening exercise program

taught by his physical therapist, and use of relaxation techniques. In addition, if pain is severe enough to prevent usual work responsibilities, he recommends that Ben take a dose of short-acting oxymorphone 5 mg up to twice daily when BTP occurs.

During the next 3 months, Ben reports that he is satisfied with his treatment regimen and is no longer missing any work due to his pain. By adjusting his lifting technique, applying the lidocaine patch, and prophylactically taking oxymorphone 5 mg, he is able to complete all of his work-related required tasks and he is sleeping well. His mood is greatly improved since he has regained intimacy with his wife and can engage in activities with his children.

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