

Balancing Clinical
and Risk Management
Considerations for
Chronic Pain Patients
on Opioid Therapy

CME

Monograph



AMERICAN ACADEMY OF
FAMILY PHYSICIANS

Balancing Clinical and Risk Management Considerations for Chronic Pain Patients on Opioid Therapy

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Learning Objectives

After reading this monograph, family physicians should be able to:

1. Evaluate patients who have chronic nonmalignant pain in order to select appropriate candidates for opioid treatment.
2. Balance the risk of drug addiction, diversion and other problematic behaviors with the likelihood of being able to effectively manage patients' pain.
3. Implement a structured treatment protocol

Introduction

Chronic nonmalignant pain is a growing concern for America's family physicians. For the purposes of this monograph, hereafter "chronic pain" refers to chronic pain of nonmalignant origin. A 2005 survey found that 19 percent of American adults reported suffering from chronic pain, and another 34 percent reported recurrent pain. The same survey suggests that this pain is also somewhat undertreated: While some 63 percent of patients said that they had spoken to their physician about their pain, only 31 percent reported complete relief, and 21 percent reported little to no relief.¹

When patients have not made adequate progress toward achieving treatment goals through non-pharmacologic and nonopioid treatment, physicians may consider a trial of opioid therapy. However, problematic behaviors, including diversion (the exchange of legally obtained opioids for money or illegal services) and addiction can overshadow the positive role opioids can play for some patients who have chronic pain. Family physicians may be reluctant to open themselves and their practices up to the kind of problems that may be associated with opioid prescribing. Indeed, these problems cannot be completely avoided without refusing to prescribe opioids altogether. The underutilization of opioids, however, can lead to undertreatment and unnecessary patient suffering.²

Concerns about the safety and efficacy of opioid treatment may also give physicians pause. Total opioid deaths increased from 3,543 in 1999 to 9,091 in 2004,³ and the long-term use of opioids, even at high doses, may not eliminate all pain in some patients. One meta-analysis of studies on opioid treatment for chronic back pain showed that opioids may be efficacious in the short term (<16 weeks), but long-term efficacy was unclear.⁴ Patients whose pain does not respond fully to opioid treatment may remain in the category of incomplete relief.

Thorough and systematic evaluation, communication, goal-setting and monitoring can help physicians manage their patients' pain while minimizing

that incorporates regular assessment of effectiveness; progress toward treatment goals; and need for adjustments, including possible change or discontinuation of opioid therapy when it is ineffective or when there are significant problems.

4. Develop a system to ensure periodic monitoring of patients in order to measure adherence.

possible opioid misuse and/or problematic behaviors. This monograph offers a practical approach to building office systems that support lower-risk prescribing and monitoring practices for family physicians who prescribe opioids for the treatment of chronic pain.

Before taking on the challenges of opioid prescribing in your practice (or even with a particular patient), the authors of this monograph urge you to ask yourself a few questions:

1. Do I have the time and the interest to devote to thorough initial evaluation of patients who may benefit from opioid therapy? Likewise, do I have the time and interest to devote to proper monitoring and follow-up with these patients? Any time "saved" by neglecting the initial evaluation or appropriate follow-up may be spent later managing patients' problematic behavior.

2. Does my office have the appropriate systems in place to support the management of patients on opioid therapy? If not, is the practice willing and able to implement these systems? These systems may include the availability of frequent appointments for patients on opioid therapy and time allotted for physician-patient phone consultations.

3. Do I have access to a consultant who can support me and my patient during opioid therapy and who can accept referrals when necessary? This consultant may specialize in pain and/or addiction. Family physicians who prescribe opioids for chronic pain may also want to work with a physician who can prescribe buprenorphine/naloxone (Suboxone). (For more about buprenorphine/naloxone prescribing, see sidebar, p. 18.)

Family physicians who answer these questions affirmatively should feel confident in their practices' ability to manage patients on opioid therapy. Physicians who do not have the necessary time, interest and resources—and access to a trusted consultant—may want to consider sending their patients elsewhere for opioid treatment.

Evaluating the Patient Who Has Chronic Pain

A comprehensive patient history and physical examination, including rigorous documentation thereof, is the first step in evaluating a patient for possible opioid therapy.⁵ The documentation should include⁶:

- The nature and intensity of the pain.
- Current and past pharmacologic and nonpharmacologic treatments (including dosages) and their relative effectiveness.
- Underlying and coexisting diseases or conditions, especially major depressive disorder, which, according to one study, has a prevalence of 52 percent amongst patients who have chronic pain.⁷
- The effect of pain on physical and psychological function. (The Pain Disability Index [Figure 1] is useful for determining baseline function and can be revisited during treatment to measure functional improvement.)
- History of past or current substance abuse.
- The presence of one or more recognized medical indications for the use of a controlled substance.

Patient records (from the current practice and any previous providers and pharmacies, if possible) should be reviewed in addition to relying on the patient's memory and reporting. Any current opioid use should be identified and discussed, as patients who are being evaluated for ongoing opioid therapy may already be receiving treatment for acute pain, or may be seeking an adjustment to treatment for chronic pain. If another provider has prescribed opioids for a patient, complete records should be obtained and the patient's pain complaint should be fully reevaluated before continuing opioid treatment. A telephone call to the physician who gave the patient his or her most recent prescription can be very useful and can help avoid multiple prescriber situations. Even if this physician is not available to talk by telephone, other staff members at the practice may be able to give relevant information, such as when the patient was last seen in the office and the most recent opioid dosage. (When speaking with a patient's previous provider, family physicians should remain mindful of Health Insurance Portability and Accountability Act [HIPAA]-related privacy concerns.) Some patients may be distressed by the idea that your practice will be calling the previous practice; in these cases, it is appropriate to suspect addiction or other aberrant behaviors.

Substance Abuse History

When reviewing a patient's history of substance abuse, ask about any personal or family history of abuse, including alcoholism, illegal drug use and prescription drug abuse. Prior personal substance

abuse problems may be linked to opioid abuse. One study, which studied patients with AIDS-related pain and a history of substance abuse (n=73) and patients with cancer-related pain and no history of substance abuse (n=100), found that patients who had a substance-abuse history were more than twice as likely to exhibit aberrant drug-taking behaviors than patients without this history.⁸

Urine drug testing (UDT) may be appropriate during the initial evaluation of patients being considered for opioid therapy.⁹ Testing all patients introduces the idea of urine testing so that future testing for monitoring purposes may seem more routine. For patients who report current opioid therapy, UDT can be used to measure adherence, verify patients' honesty about current drug use and rule out the use of other illicit or unprescribed licit drugs. If the patient's UDT reveals illicit drug use, he or she should be further assessed for substance abuse disorders.⁹ (For more about UDT, see "Periodic Review," p. 16.)

Generally, and unless they are already very familiar with a particular patient's substance abuse history, physicians should screen patients for possible substance abuse problems before prescribing opioids. Evaluating this risk can help determine which patients need special care and more rigorous follow-up and, in some cases, a referral to a subspecialist who is skilled in pain and addiction. (See "Triaging Patients Based on Risk," p. 9.) In some cases, simply asking a patient and his or her family members about past and current drug and alcohol problems may clarify the situation. For example, a recovering alcoholic may volunteer information about his or her past addiction and express concern about becoming addicted to opioids.

Several tools to help assess potential substance abuse risk are available. The simplest of these may be a version of the CAGE questionnaire adapted to include drugs (CAGE-AID) (Figure 2).¹⁰ The CAGE-AID questionnaire is simple enough for physicians and support staff to memorize and can be informally administered during an office visit. (Patients may also self-administer the tool and share their responses with a physician or nurse.) According to one study, the CAGE-AID questionnaire's sensitivity was .70 and its specificity was .85 for drug abuse when two or more affirmative responses were defined as a positive result; when only one affirmative response was defined as positive, sensitivity rose by 13 percent, but specificity dropped by 10 percent.¹⁰ According to the U.S. Preventive Services Task Force, screening tools for drug use or misuse such as the CAGE-AID, when applied across the general population have, at best, a posi-

Figure 1. Pain Disability Index

Name: _____ Date: _____

Pain Disability Index: The rating scales below are designed to measure the degree to which aspects of your life are disrupted by chronic pain. In other words, we would like to know how much your pain is preventing you from doing what you would normally do, or from doing it as well as you normally would. Respond to each category by indicating the overall impact of pain in your life, not just when the pain is at its worst.

For each of the seven categories of life activity listed, please circle the number on the scale which describes the level of disability you typically experience. A score of 0 means no disability at all, and a score of 10 signifies that all of the activities in which you would normally be involved have been totally disrupted or prevented by your pain.

Family/home responsibilities: This category refers to activities related to the home or family. It includes chores or duties performed around the house (e.g., yard work) and errands or favors for other family members (e.g., driving the children to school).

No disability 0 1 2 3 4 5 6 7 8 9 10 Worst disability

Recreation: This category includes hobbies, sports and other similar leisure time activities.

No disability 0 1 2 3 4 5 6 7 8 9 10 Worst disability

Social Activity: This category refers to activities that involve participation with friends and acquaintances other than family members. It includes parties, theater, concerts, dining out and other social functions.

No disability 0 1 2 3 4 5 6 7 8 9 10 Worst disability

Occupation: This category refers to activities that are a part or directly related to one's job. This includes nonpaying jobs as well, such as that of a housewife or volunteer worker.

No disability 0 1 2 3 4 5 6 7 8 9 10 Worst disability

Sexual behavior: This category refers to the frequency and quality of one's sex life.

No disability 0 1 2 3 4 5 6 7 8 9 10 Worst disability

Self-care: This category includes activities that involve personal maintenance and independent daily living (e.g., taking a shower, driving, getting dressed, etc.)

No disability 0 1 2 3 4 5 6 7 8 9 10 Worst disability

Life-support Activities: This category refers to basic life-supporting behaviors such as eating, sleeping and breathing.

No disability 0 1 2 3 4 5 6 7 8 9 10 Worst disability

Reprinted with permission from Pollard CA. The relationship of family environment to chronic pain disability. (Doctoral dissertation, California School of Professional Psychology—San Diego) Dissertation Abstracts International 1981;42,2077B.

tive predictive value of 83 percent.¹¹ When used in a high-risk population, the positive predictive value is likely higher.

As a practical matter, one affirmative response may “raise a red flag” when the CAGE-AID is administered. Two or more affirmative responses may be seen as an indication of increased risk of opioid abuse.

Past alcohol abuse may also predict opioid misuse in patients who have chronic pain. One prospective study of 196 patients enrolled in a chronic pain disease management program found that 44 percent of patients who misused opioids had a history of alcohol abuse.¹² All patients should be screened for alcohol use disorders prior to initiating opioid therapy. The 10-question Alcohol Use

Figure 2. The CAGE Questions Adapted to Include Drugs (CAGE-AID)

1. Have you ever felt you ought to **C**ut down on your drinking or drug use?
2. Have people **A**nnoyed you by criticizing your drinking or drug use?
3. Have you ever felt bad or **G**uilty about your drinking or drug use?
4. Have you ever had a drink or used drugs first thing in the morning as an **E**ye opener to steady your nerves or to get rid of a hangover?

Adapted with permission from Brown RL, Rounds LA. Conjoint screening questionnaires for alcohol and other drug abuse: criterion validity in a primary care practice. Wis Med J 1995;94:135-40.

Figure 3. Alcohol Use Disorders Identification Test (AUDIT)

PATIENT: Because alcohol use can affect your health and can interfere with certain medications and treatments, it is important that we ask some questions about your use of alcohol. Your answers will remain confidential, so please be honest.

Place an X in one box that best describes your answer to each question.

Questions	0	1	2	3	4
1. How often do you have a drink containing alcohol?	Never	Monthly or less	2 to 4 times a month	2 to 3 times a week	4 or more times a week
2. How many drinks containing alcohol do you have on a typical day when you are drinking?	1 or 2	3 or 4	5 or 6	7 to 9	10 or more
3. How often do you have 5 or more drinks on one occasion?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
4. How often during the last year have you found that you were not able to stop drinking once you started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
5. How often during the last year have you failed to do what was normally expected of you because of drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
7. How often during the last year have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
8. How often during the last year have you been unable to remember what happened the night before because of your drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
9. Have you or someone else been injured because of your drinking?	No		Yes, but not in the last year		Yes, during the last year
10. Has a relative, friend, doctor or other health care worker been concerned about your drinking or suggested you cut down?	No		Yes, but not in the last year		Yes, during the last year
Total					

Scoring: Record the score for each response in the blank box at the end of each line, then total these numbers. Total scores of 8 or more for men up to age 60 or 4 or more for women, adolescents and men over 60 are considered positive screens. For patients with totals near the cut-points, clinicians may wish to examine individual responses to questions and clarify them during the clinical examination.

Adapted from the National Institute on Alcohol Abuse and Alcoholism. Helping patients who drink too much: a clinician's guide; 2005. Available at: http://pubs.niaaa.nih.gov/publications/Practitioner/CliniciansGuide2005/clinicians_guide.htm.

Figure 4.
Opioid Risk Tool (ORT)

Item	Mark each box that applies	F	M
1. Family history of substance abuse			
Alcohol	<input type="checkbox"/>	1	3
Illegal drugs	<input type="checkbox"/>	2	3
Prescription drugs	<input type="checkbox"/>	4	4
2. Personal history of substance abuse			
Alcohol	<input type="checkbox"/>	3	3
Illegal drugs	<input type="checkbox"/>	4	4
Prescription drugs	<input type="checkbox"/>	5	5
3. Age (mark box if 16-45)			
	<input type="checkbox"/>	1	1
4. History of preadolescent sexual abuse			
	<input type="checkbox"/>	3	0
5. Psychological disease			
ADD, OCD, bipolar disorder, schizophrenia	<input type="checkbox"/>	2	2
Depression	<input type="checkbox"/>	1	1

Total

Total score risk category:

0-3: Low risk (unlikely to abuse opioids)

4-7: Moderate risk (as likely will as won't abuse opioids)

≥8: High risk (likely to abuse opioids)

F = female; M = male; ADD = attention-deficit disorder; OCD = obsessive-compulsive disorder.

Adapted with permission from Webster LR, Webster RM. Predicting aberrant behaviors in opioid treated patients: preliminary validation of the opioid risk tool. Pain Med 2005;6:432-442.

Disorders Identification Test (AUDIT) (Figure 3) focuses on the frequency and quantity of the patient's drinking, and consequences associated with drinking.

A physician who administers the AUDIT questionnaire should carefully review the patient's answers to individual questions in addition to the overall score. Positive answers to all questions should be discussed with the patient. Answers that indicate binge drinking are of particular concern, as this may indicate that the patient cannot control his or her drinking. All patients who take opioids should be advised not to drink when taking their pain medication.

The Opioid Risk Tool (ORT) was developed and validated specifically to assess risk that a patient will display aberrant behaviors associated with opioid abuse (Figure 4). Unlike some other risk assessment tools, the ORT does not simply measure past patient behavior as an indicator of risk. The ORT displayed 85 percent discrimination for female patients, and 82 percent for male patients.¹³

Of course, even with screening tools such as the CAGE-AID, the AUDIT, the ORT and others, it is not always possible to predict which patients will abuse opioids. No screening tool is 100 percent predictive, and patients may be reluctant to complete these screening questionnaires or answer questions related to past substance misuse out of fear of being denied treatment.⁹ To help avoid this, patients can be told prior to administering the screening questionnaires that previous problems with substance abuse may not necessarily exclude them from opioid therapy; rather, they may still receive opioids, but the treatment plan and monitoring may be enhanced to secure their safety.

In addition to talking with previous prescribers, urine drug testing and administering these screening tools, it may be helpful to talk with a patient's family members before prescribing opioids in order to determine whether any past or current substance abuse or misuse may exist.

Balancing Benefit and Risk

Opioid therapy is appropriate when the potential benefit of pain relief outweighs the potential risks associated with this type of therapy. However, there is not a simple equation to solve this clinical question. A patient whose diagnosis suggests that his pain could respond well to opioid treatment should not necessarily be excluded from this treatment solely because he shows an increased risk of problematic behavior. (This patient would either be monitored more closely than his lower-risk counterparts or referred to a pain specialist.) Conversely, a patient exhibiting moderate risk of aberrant behaviors but who has a diagnosis unlikely to respond well to opioid therapy (such as fibromyalgia,¹⁴ recurrent headaches¹⁵ or irritable bowel syndrome¹⁶) may not be a good candidate for treatment with opioids.

The DIRE Score

In response to the need to determine which patients make the best candidates for opioid therapy, one physician group developed the DIRE Score. The DIRE Score was designed for use in primary care practices treating patients who have chronic non-malignant pain; it can be applied to patients who are already receiving opioid therapy or who are being considered for opioid treatment. The score is used to predict the potential efficacy of analgesia and potential patient adherence to long-term opioid treatment. Four factors—diagnosis, intractability, risk and efficacy—are considered separately and rated; the sum of these ratings determines the DIRE Score (*Figure 5*).

The DIRE Score was shown to be valid and reliable in a retrospective trial, and the Score was strongly correlated with compliance with opioid treatment. The Score correlated moderately with efficacy of treatment. Intractability was not correlated with efficacy, which was not surprising because efficacy is, by definition, difficult to achieve in intractable conditions. The Diagnosis score did not correlate with successful outcomes, but was retained as a criterion for selecting patients for opioid therapy in order to emphasize the importance of not prescribing long-term opioids in patients without diagnoses or whose conditions are not associated with moderate to severe pain.¹⁷

The DIRE Score's dependence on physicians' subjective assessment may limit its practical application. Nevertheless, the concept of reviewing and examining the patient's diagnosis, the intractability or severity of the pain, the risk of potential problematic behavior and the efficacy of previous treatments is a valuable one. Not only can it help family physicians determine whether to consider

opioid therapy for a particular patient, it can also help identify patients who may need more rigorous oversight throughout the treatment process. Patients who have a low or borderline DIRE Score may benefit from referral to a multidisciplinary pain clinic.

Triaging Patients Based on Risk

Based on the initial patient evaluation balanced with other clinical considerations, most patients can be categorized in one of three basic groups:⁹

Group I (low risk)

Generally, these patients have neither a past nor current history of personal substance abuse nor a significant family history. They also lack a major or untreated psychiatric disorder.⁹ Family physicians who are well equipped to prescribe opioids and monitor their use should feel comfortable treating these patients. A goal-directed treatment plan, including a standard informed consent and a patient agreement (see p. 12), should be initiated before the opioid trial begins. Patients in Group I may require less monitoring than patients who are designated as higher-risk; however, these patients—like all patients on opioid therapy—should visit the practice regularly (weekly or monthly during initiation and titration of treatment, and at least every three months when on a stable dose) to review treatment goals and to ensure adherence.

Group II (intermediate risk)

Typically, patients who have a past history of substance abuse, or who have a contributory family history of substance abuse, fall into this group. These patients may also have a past or current psychiatric disorder.⁹ If the past abuse occurred with a drug other than an opioid, family physicians may want to treat these patients in their practice, but with caution. (A past history of opioid abuse puts a patient in Group III.) As with the patients in Group I, these patients must complete and adhere to a goal-directed treatment plan. However, these patients must also agree to more frequent office visits and may have to submit to more rigorous monitoring, such as UDT or pill counts. Physicians may be more comfortable comanaging patients in this group with an addiction subspecialist or other consultant.⁹

Group III (high risk)

Patients who have an active substance abuse disorder (including alcoholism or opioid addiction)

and/or a major, untreated psychiatric problem comprise the high-risk group. These patients pose a substantial risk to themselves, to others and to the physicians who treat them, and should generally be treated by subspecialists and not in a family physician's office.⁹

Patients who have a previous opioid-abuse problem also fall into this category. While patients

who have a history of substance abuse require careful monitoring, such a history is not an absolute contraindication for opioid treatment.⁹ Family physicians who refer patients who have a history of substance abuse to a subspecialist may want to assure them that they *may* be able to receive opioid treatment, but they won't be receiving it in the primary care setting.

Figure 5.

DIRE Score: Patient Selection for Chronic Opioid Analgesia

Score	Factor	Explanation
	Diagnosis	<p>1 = Benign chronic condition with minimal objective findings or no definite medical diagnosis. Examples: fibromyalgia, migraine headaches, nonspecific back pain.</p> <p>2 = Slowly progressive condition concordant with moderate pain, or fixed condition with moderate objective findings. Examples: failed back surgery syndrome, back pain with moderate degenerative changes, neuropathic pain.</p> <p>3 = Advanced condition concordant with severe pain with objective findings. Examples: severe ischemic vascular disease, advanced neuropathy, severe spinal stenosis.</p>
	Intractability	<p>1 = Few therapies have been tried and the patient takes a passive role in his/her pain management process.</p> <p>2 = Most customary treatments have been tried but the patient is not fully engaged in the pain management process, or barriers prevent (insurance, transportation, medical illness).</p> <p>3 = Patient fully engaged in a spectrum of appropriate treatments but with inadequate response.</p>
	Risk:	(R = Total of P + C + R + S below)
	Psychological	<p>1 = Serious personality dysfunction or mental illness interfering with care. Example: personality disorder, severe affective disorder, significant personality issues.</p> <p>2 = Personality or mental health interferes moderately. Example: depression or anxiety disorder.</p> <p>3 = Good communication with clinic. No significant personality dysfunction or mental illness.</p>
	Chemical Health	<p>1 = Active or very recent use of illicit drugs, excessive alcohol or prescription drug abuse.</p> <p>2 = Chemical copper (uses medications to cope with stress) or history of chemical dependency in remission.</p> <p>3 = No chemical dependency history. Not drug-focused or chemically reliant.</p>
	Reliability	<p>1 = History of numerous problems: medication misuse, missed appointments, rarely follows through.</p> <p>2 = Occasional difficulties with compliance, but generally reliable.</p> <p>3 = Highly reliable patient with medications, appointments and treatment.</p>
	Social Support	<p>1 = Life in chaos. Little family support and few close relationships. Loss of most normal life roles.</p> <p>2 = Reduction in some relationships and life roles.</p> <p>3 = Supportive family/close relationships. Involved in work or school and no social isolation.</p>
	Efficacy Score	<p>1 = Poor function or minimal pain relief despite moderate to high doses.</p> <p>2 = Moderate benefit with function improved in a number of ways (or insufficient information—hasn't tried opioid yet or very low doses or too short of a trial).</p> <p>3 = Good improvement in pain and function and quality of life with stable doses over time.</p>

For each factor, rate the patient's score from 1-3 based on the explanations in the right-hand column.

Total score = D + I + R + E.

Score 7-13: Not a suitable candidate for long-term opioid analgesia.

Score 14-21: Good candidate for long-term opioid analgesia.

Adapted with permission from Belgrade MJ, Schamber CD, Lindgren BR. The DIRE score: predicting outcomes of opioid prescribing for chronic pain. J Pain 2006;7(9):671-81.

Naturally, patients who have been categorized in a certain group can move to another one. The line between Groups II and III is especially fluid; patients can slip from Group II to Group III if they relapse into active addiction, and someone in Group

III may move to Group II with appropriate substance abuse treatment.⁹ For this reason, following a careful plan for periodic monitoring (see p. 16), even with patients who initially fit into Group I, is critical.

The Goal-directed Treatment Plan

Once a physician decides that a risk/benefit assessment makes a patient a candidate for a trial of opioid therapy, the physician and patient should discuss and draw up a written treatment plan. The plan should contain an individualized and agreed-upon goal for treatment so the physician and patient can recognize whether the treatment is a success.⁶ “Success” may be defined as tolerable pain and improved physical and psychosocial function,⁶ and will necessarily differ for each patient. A patient who has severely debilitating pain, for example, may have a goal of getting out of bed to join her family for one meal each day. A patient who suffers from a back injury, on the other hand, may set a goal of returning to work within 12 weeks. It is up to the physician and the patient to decide together what may or may not be realistically achieved through opioid treatment. Revisiting the Pain Disability Index (*Figure 1*) regularly with a patient can help identify whether function has improved. When there is no indication of improved function, the treatment should be reassessed and adjusted.

The treatment plan should also include information about plans for any further diagnostic evaluations, nonopioid treatment modalities and/or rehabilitation programs, when appropriate.⁶

Informed Consent and Treatment Agreement

Before a trial of opioid therapy is initiated, the physician must ensure that the patient (or the patient’s guardian) has been informed of the potential risks and benefits of opioid use.⁵ Patients should be informed of the risk of sedation, decreased respiration, constipation, nausea and vomiting, as well as the risk of impairment, opioid’s effect on the ability to drive or operate machinery, and potential interactions with other medications and alcohol. Pregnant women who are being considered for opioid therapy should be told that their infants may be dependent on opioids at birth. The initial patient consultation and the informed consent form should include information for the patient about the probability of dependence on opioids and the withdrawal symptoms he or she may feel if opioid treatment is discontinued. The possibility of addiction should also be explained, and physicians should use patient-friendly language that urges the patients to tell their physician if they begin using their opioid medication to feel high or relieve stress, or if they become fixated on obtaining additional medication. Patients should also understand that their treatment with opioid therapy is a *trial*, and that the therapy may need to be changed if sufficient progress toward goals is not

made. Finally, physicians should explain that opioids are prescribed to reduce pain and improve function, and may not eliminate pain completely.

Sharing detailed information with the patient about the potential benefits and risks of opioid therapy brings the patient into the decision-making process. One suggested approach is to give the patient an information sheet outlining these benefits and risks, to discuss it with him or her and to allow the patient to take it home to review it with a spouse or another family member before the physician will write the prescription. In one of this monograph’s author’s experience, fully half of patients who received this detailed explanation decided to decline opioid treatment.

Patients should also be made aware of the conditions under which opioids will be prescribed, including the physician’s roles and responsibilities as a prescriber and the practice’s policy on monitoring patients who are taking opioids for chronic pain. A written agreement between the physician and the patient should spell out the patient’s responsibilities, which may include:¹⁸

- Agreeing not to seek opioids from another physician or practice.
- Filling opioid prescriptions through only one pharmacy.
- Taking steps to guarantee the safety and security of the patient, his or her family and the community, by ensuring the opioid medication does not fall into the hands of others, either directly (by sharing or selling the medication) or indirectly (by allowing others—especially children and teenagers—to have access to the pill bottles).
- Providing samples when the practice requests urine or serum toxicology screens.
- Being available for additional unscheduled visits, which may include pill counts, to ensure safety.
- Agreeing to follow the policies of the practice by keeping appointments, refraining from seeking early refills, etc.
- Acknowledging that initial opioid treatment is on a trial basis and may be discontinued if treatment goals are not met.

All patients on opioid therapy should adhere to these basic responsibilities; some monitoring may need to be more stringent, depending on the patient’s risk of problematic behavior. A signed agreement that includes specific patient goals is a valuable “contract” that can be revisited if problematic behaviors arise or if treatment is not successful. Sample informed consent forms and treatment agreements are available in English and in Spanish on the American Academy of Pain Medicine’s Web site: http://www.painmed.org/clinical_info/guidelines.html.

The Opioid Trial

For patients who are not currently taking opioids, treatment should be initiated at the lowest standard dose and progressively and carefully titrated until adequate analgesia is met, or until adverse effects become unacceptable and require a reevaluation of treatment.¹⁹ Standard first doses of opioids commonly used to treat chronic pain are listed in *Table 1*.

Some patients may respond to low-dose, short-acting opioids for chronic pain. Patients who have sustained pain may need longer-acting agents. Evidence that the specific analgesic formulation or dosing schedule affects efficacy or addiction risk is unclear; therefore, the regimen should be selected based on the patient's pain complaint, lifestyle and preferences.¹⁹ Generally speaking, long-acting opioids taken around-the-clock should form the basis of chronic opioid therapy for patients who have sustained pain. Scheduled long-acting opioids have the advantage of producing a steady state, without the cycling effect of pain relief and withdrawal associated with short-acting opioids, which could, theoretically, lead to problematic behavior patterns. However, there may be a tendency to use more drug than is actually needed, and adaptations to the steady state (e.g., tolerance) may ultimately decrease efficacy.²⁰ Short-acting opioids may be prescribed in addition to long-acting for breakthrough pain, but should not be dispensed in large numbers in order to deter potential abuse or diversion.

For patients for whom an effective dosage has been established, a "maintenance" phase may be initiated. During this phase, the effective dosage is continued and patients should adhere to standard follow-up procedures as outlined in the treatment agreement (see "Periodic Review," p. 16).

Opioid Rotation

When patients do not achieve satisfactory analgesia despite numerous trials of dose escalation, or when a particular opioid's side effects are intolerable, opioid rotation is an option. Opioid rotation involves discontinuing one opioid and replacing it with another. While this strategy is widely accepted for addressing refractory pain in patients who have cancer,²¹ its use in treating chronic pain shows potential but has not been formally validated.¹⁹

Generally, in opioid rotation, the second opioid can be started at half the equianalgesic dose of the current dose of the first because of incomplete cross-tolerance.¹⁹ Incomplete cross-tolerance occurs when a patient has developed a tolerance to the analgesia of the first drug; their tolerance may not be present to the same degree with the second. Once the first opioid has been discontinued completely, the dose

of the second opioid may be increased slowly until optimal analgesia is obtained.¹⁹ However, during dose escalation, it is important to keep in mind that while the second opioid may provide more analgesia, it may also come with adverse effects.

As a practical matter, substituting a long-acting agent such as fentanyl transdermal system (Duragesic) or methadone (Dolophine, Methadose) for short-acting formulations of drugs such as morphine or oxycodone (ETH-Oxydose, OxyFAST, OxyIR, M-oxy, Roxicodone) may provide relief to patients whose pain does not respond to the short-acting agents.

Methadone is an attractive candidate for opioid rotation because, for reasons that are not fully understood, a rotation to very-low-dose methadone usually produces surprisingly good analgesia. It is also less expensive than many other opioids.¹⁹ Methadone can often be started at as low as one-tenth the equianalgesic dose of the first opioid, but because the conversion ratio depends on many factors, including length of prior treatment, determining the appropriate equivalent dose can be a challenge. The use of methadone in the treatment of chronic pain comes with some additional risks. See the sidebar for more information about prescribing methadone.

Prescribing Methadone for Chronic Pain

Methadone is most commonly associated with the treatment of opioid addiction, but its analgesic effects may also be useful for the treatment of chronic pain. Lower doses of methadone may be considered when the adverse effects of other opioids limit escalating the dosages of these opioids. Because it is a synthetic analgesic, it may also be used by patients who are allergic to other opioids.²² Finally, methadone may be a good choice for patients who have neuropathic pain because of its N-methyl-D-aspartate (NMDA)-receptor-antagonist activity.²³

That said, the use of methadone is not without caveats. While it is prescribed once a day for opioid addiction, methadone must be taken every eight hours to achieve a sustained analgesic effect. Its long plasma half-life (mean = 26.8 hours), combined with this dosing schedule, can cause toxic accumulation.²³ Toxicities may include respiratory depression and cardiac dysrhythmias (torsades de pointe).

The 2003 National Assessment of Methadone-Associated Mortality found that deaths associated with methadone have dramatically increased in recent years. In 2001, more methadone-associated deaths were reported than during the entire reporting period lasting from 1990 to 1999.²⁴ Citing these deaths, as well as the risk of respiratory depression and QT-interval prolongation, the U.S. Food and Drug Administration (FDA) added a warning to methadone's label in 2006. The warning urges vigilance during treatment initiation, dose titration and conversion from one opioid to another, and states that methadone should only be used for analgesic therapy when its benefits clearly outweigh its risks.²⁵

Methadone is metabolized in the liver by the type I cytochrome P450 (CYP450) enzymes, and there can be considerable genetic variability in individuals' ability to metabolize this drug. In addition, there is a long list of drugs that interact with methadone, including some antiepileptics, selective serotonin reuptake inhibitors (SSRIs), benzodiazepines, some antibiotics and antivirals, and many others.²³

Table 1.

Dosages and Titration Information for Selected Opioids*

Short-acting Opioid	Initial Dosage	Dosage Titration
Codeine (alone or in combination with APAP [Fioricet, Phenaphen 4, Tylenol 2, Tylenol 3, Tylenol 4] or ASA [Aspirin 3, Aspirin 4, Empirin 3, Empirin 4, Fiorinal])	30 mg orally every 4 to 6 hours	Increase dose as needed and tolerated to a maximum of 360 mg/day (4000 mg/day APAP†). Ceiling effect occurs at doses > 60 mg/dose.
Hydrocodone (in combination with APAP [Anexsia, Bancap, Ceta-Plus, Co-Gesic, Duocet, Dolacet, Hydrocet, Hydrogesic, Hy-Phen, Lorcet, Lortab, Margesic, Norco, Panacet, Stagesic, T-Gesic, Vicodin, Zydone], ASA [Alor 5, Azdone, Damason-P, Lortab ASA, Panasal 5] or IBU [Vicoprofen])	5 to 10 mg orally every 4 to 6 hours	Increase dose as needed and tolerated. Maximum dose: 60 mg/day (4000 mg/day APAP†) for hydrocodone + APAP combination <i>or</i> 37.5 mg/day (1000 mg/day IBU) for hydrocodone + IBU combination
Hydromorphone (Dilaudid)	2 mg orally every 4 to 6 hours	Individually titrate as needed and tolerated; doses ≥ 4 mg every 4 to 6 hours may be necessary.
Morphine	10 to 30 mg orally every 4 hours	Individually titrate as needed and tolerated.
Oxycodone (ETH-Oxydose, OxyFAST, OxyIR, M-oxy, Roxicodone) (alone or in combination with APAP or ASA)	5 mg orally every 6 hours	Increase dose as needed and tolerated. For combination products, maximum dose is limited by APAP or ASA content (4000 mg/day for both†).
Oxymorphone IR (Opana)	10 to 20 mg every 4 to 6 hours	Titrate based on patient's response to the initial dose.
Long-acting Opioid	Initial Dosage	Dosage Titration
Fentanyl Transdermal System (Duragesic)‡	25 mcg/hour every 72 hours	Increments should be based on supplemental opioid doses, using a ratio of 25 mcg/hour fentanyl for every 90 mg/24 hours of supplemental oral morphine equivalent. Make increments at least 3 days after initial dose, then not more often than every 6 days thereafter as necessary.
Methadone (Dolophine, Methadose)	2.5 mg orally every 6 to 8 hours	Increments of 2.5 mg every 8 hours may be made every 5 to 7 days.
Morphine CR (MS Contin, Oramorph)	15 mg orally every 24 hours	Total daily increments of < 30 to 40 mg/day may be made every 2 days.
Morphine SR	15 mg orally every 12 hours	
	20 mg orally every 24 hours	
Morphine ER (Avinza, Kadian)	30 mg orally every 24 hours	
Oxycodone CR (Oxycontin)	10 mg orally every 12 hours	May increase to 20 mg every 12 hours after 1 or 2 days. Thereafter, the total daily dose may be increased by 25% to 50% of the current dose every 1 or 2 days.
Oxymorphone ER (Opana ER)	5 mg every 12 hours	Titrate at increments of 5 to 10 mg every 12 hours every 3 to 7 days.

*—For opioid-naïve adults (70 kg). See note about fentanyl transdermal system.

†—The APAP dosage for chronic alcoholics should not exceed 2000 mg/day.

‡—Fentanyl transdermal system not for use in opioid-naïve patients. A 12.5 mcg/hour patch is also available, and should be used when 25 mcg/hour patch may not be tolerated (e.g., in young and elderly patients).

APAP = acetaminophen; ASA = acetylsalicylic acid; CR = controlled release; ER = extended release; IBU = ibuprofen; IR = immediate release; SR = sustained release

Adapted from Department of Veterans Affairs and Department of Defense. VA/DoD clinical practice guideline for the management of opioid therapy for chronic pain. Washington, D.C.: Department of Veterans Affairs and Department of Defense; 2003. Available at: <http://www.ihp.gov/nonmedicalprograms/nc4/documents/chronicpainguidelinesva2003.pdf>. Additional information from Drug facts and comparisons. St. Louis: Drug Facts and Comparisons; 2008.

Discontinuing Opioid Therapy

A physician and patient may consider discontinuation of opioid therapy for several reasons:²⁶

- Treatment goals in the form of satisfactory analgesia have not been achieved after several dose adjustments over several weeks and/or after opioid rotation;
- Side effects are not acceptable to the patient or the physician;
- The underlying pain has improved as a result of surgery or other interventions;
- The patient prefers not to continue therapy for emotional, social or financial reasons.

Physicians may also choose to pursue discontinuation because of concerns about efficacy or patient nonadherence. In addition, potential hormonal problems or other safety concerns—including opioid-induced hyperalgesia (that is, an increased sensitivity to pain)—may cause a physician to consider discontinuation of therapy.²⁶ One small study (n = 6) found that patients may experience opioid-induced hyperalgesia as early as one month after initiation of opioid therapy.²⁷

Safely tapering opioids can be complex and depends largely on the patient's clinical situation. Several tapering options are available, but as a general rule, the simplest and safest taper is a dose reduction of 10 percent to 20 percent per week. For an in-depth discussion of discontinuing therapy, see the online article "Opioid Tapering: Safely Discontinuing Opioid Analgesics" at http://pain-topics.org/pdf/Safely_Tapering_Opioids.pdf.

Nonpharmacologic alternative therapies may be useful during discontinuation. In one very small study (n = 7), patients suffering from chronic pain and using opioid analgesics were weaned from their medication. During and after detoxification, these patients were taught muscular relaxation techniques and were given supportive therapy consisting of encouraging statements and (when requested) discussion of their problems. Most of these patients showed a statistically significant decrease in self-reported pain immediately after detoxification and at a six-month follow-up.²⁸

If the patient is reluctant to discontinue opioids despite an apparent lack of efficacy, the treatment agreement and goals should be reviewed and he or she should be reminded that the opioid trial was just that—a trial. During discussions about possible discontinuation, physicians should be on the lookout for aberrant behavior suggestive of noncompliance and/or abuse. (See "Recognizing Tolerance, Dependence, Pseudoaddiction and Addiction," p. 16.)

It is important to treat potential addiction as you would any other medical problem—listen to the patient, assess and refer, when needed. It may be necessary to tell the patient, "I do not feel comfortable treating you while this behavior persists. I would like to refer you to someone else to continue your treatment." Refer the patient to a mental health or substance abuse professional, or to a family physician who can prescribe buprenorphine/naloxone. (See sidebar, "Using Buprenorphine/Naloxone to Manage Opioid Addiction," p. 18.)

Periodic Review

Management of opioid therapy requires regular monitoring to measure patient adherence and progress toward the therapeutic goals. Physicians should meet with patients on a regular basis—some of these visits can occur by phone, but established patients on opioid therapy should be seen in the office at least every three months, and more often if their dose has recently changed or if they have been determined to be higher risk.

Urine Drug Testing

When the patient and physician initially discuss opioid treatment, the patient should understand that he or she may be asked to participate in random UDT; this provision should be included in the treatment agreement. The goal of UDT is to improve patient care by protecting both the patient and the physician. UDT is an objective diagnostic test that demonstrates adherence and builds trust with the physician. It helps the physician demonstrate professional vigilance and more effectively advocate for the patient with his or her family, workplace or other interested third parties.²⁹

UDT can be easily performed by asking staff to collect a sample prior to any visit with a patient on opioid therapy. If the sample is collected at the practice, using a dye-containing toilet bowl cleaner and/or temporarily taping sink faucets can help prevent tampering.

The patient's sample is sent to the lab for quantitative analysis for the prescribed medication, qualitative analysis for drugs of abuse, and routine urinalysis to determine whether the sample provided is, in fact, urine. As the ability of any laboratory to provide these tests varies, physicians should verify a lab's policies and procedures for UDT prior to use.

While no system is "foolproof," UDT can help support the therapeutic relationship between the physician and the patient who appropriately uses opioids for their chronic pain.

The Four (Five) As

The "four As" of pain management outcomes offer an effective approach to monitoring:³⁰

- **Analgesia:** The severity of the patient's pain should be measured at baseline and at all follow-up visits. In addition to asking how the patient is feeling at today's visit (0 to 10 scale), it may be useful to ask about the best and worst days he or she experienced in the past month.

- **Activities of Daily Living:** Revisit the Pain Disability Index (*Figure 1*) with the patient and

make note of any improvement or decline in function. Functional goals should be a part of the treatment plan, and these goals in particular should be reviewed with the patient.

- **Adverse Effects:** If the patient is suffering from any adverse effects, can these be treated, or should the opioid be decreased, changed or discontinued?

- **Aberrant Behavior:** The physician should note whether any of the patient's behaviors suggest possible misuse, abuse, diversion or other problems. The Predictors of Opioid Misuse (*Table 2*) can help gauge whether a patient's patterns of behavior may indicate the need for intervention. Strategies such as pill counting and toxicology screening for drugs of abuse can be employed to monitor for adherence and the use of other drugs or medications. Documenting these results—as well as what patients report as their behavior (e.g., whether they claim to be taking the opioid as prescribed before a UDT shows otherwise)—is key to recognizing patterns of aberrant behavior and, eventually, to pursuing addiction treatment and/or legal action. Establishing an open, collaborative relationship that includes regular communication with the pharmacist or pharmacists who prescribe opioids to a clinic's patients can also help family physicians identify potential aberrant behaviors that may not be apparent during office visits.

A "fifth A" may be added to this approach—the patient's affect.⁹ Does the patient seem happier than at the last visit? Is he or she visibly distraught or depressed? Recording the physician's impression of the patient's affect over time may help identify changes in function and early signs of aberrant behavior.

Recognizing Tolerance, Dependence, Pseudoaddiction and Addiction

Tolerance, dependence, pseudoaddiction and addiction have distinct definitions, clinical implications and management.³¹

- **Tolerance:** Analgesic tolerance occurs when higher and higher doses of opioids are required to maintain the same degree of analgesic effect. Patients may also become tolerant to an opioid's adverse effects over time.³¹

- **Dependence:** Patients who are dependent on opioids will display withdrawal symptoms when the drug is abruptly stopped, reduced in dose or otherwise antagonized. Withdrawal symptoms can include worsening pain (withdrawal hyperalgesia) and feeling let down (withdrawal anhedonia), as well as the physical symptoms of withdrawal. Most

patients who take opioids on a regular basis become dependent on them.³¹ Withdrawal symptoms can generally be avoided by careful tapering of opioid therapy and, in some cases, the use of adjunctive medication.

Tolerance and dependence are normal responses that occur when certain medications—including opioids—are taken regularly. Neither should be considered evidence of substance abuse or addiction. Some patients may continue to take opioids even after their pain has resolved in order to avoid the symptoms of withdrawal; this use should not necessarily be viewed as addiction.^{20,31}

Pseudoaddiction: This term describes behaviors that may occur when a patient’s pain is undertreated. A pseudoaddicted patient may become fixated on obtaining medications, may “clock watch” or display other seemingly aberrant, drug-seeking behaviors. These patients may also obtain drugs illegally or attempt to deceive their physicians in an effort to obtain pain relief. Pseudoaddiction, unlike true addiction, resolves when the patient’s pain is effectively treated.³¹ For patients who take short-acting opioids, pseudoaddiction will often respond to switching to a long-acting agent and titrating the dose until pain is tolerable and function improves.

Addiction: A consensus document from the American Academy of Pain Medicine, the American Pain Society and the American Society of Addiction Medicine defines addiction as “a primary chronic disease ... recognized by the observation of one or more of its characteristic features: impaired control, craving and compulsive use, and continued use despite negative physical, mental, and/or social consequences.” According to the consensus document, whether or not a patient is addicted is best determined after his or her pain has been brought under control, when this is possible. A physician must use his or her clinical judgment to determine whether a patient’s behaviors indicate opioid addiction or may signal another problem, such as inadequate pain control.³¹

Physicians should suspect addiction when a patient requests rapid increases in their dosage or when a patient suddenly reports that pain that appeared to be well controlled is now intolerable. Opioid tolerance builds slowly, not rapidly. If a short-acting opioid supplements long-acting therapy to help with breakthrough pain, the short-acting pills may be used within a much shorter time period than prescribed. When opioid addiction is suspected, it is the physician’s responsibility to treat the addiction or to refer the patient to someone who can offer treatment (e.g., an addiction subspecialist, psychiatrist or a drug treatment center). Patients who are motivated to stop taking the opioid can be treated by slowly tapering the dosage and offer-

ing alternative or adjunctive treatments. It is not acceptable to simply dismiss the patient from the practice to let him or her deal with the addiction elsewhere. For this reason, it is important for family physicians to establish relationships with addiction experts who are able and willing to accept patient referrals. In some cases, and when the physician has

Table 2.
Predictors of Opioid Misuse

Illegal or Criminal Behavior

- Diversion (sale or provision of opioids to others)
- Prescription forgery
- Stealing or “borrowing” drugs from others

Dangerous Behavior

- Motor vehicle crash/arrest related to opioid or illicit drug or alcohol intoxication or effects
- Intentional overdose or suicide attempt
- Aggressive/threatening/belligerent behavior in the clinic

Behavior that Suggests Addiction

- Use of prescription medicines in an unapproved or inappropriate manner (such as cutting time-release preparations, injecting oral formulations, and applying fentanyl topical patches to oral and rectal mucosa)
- Obtaining opioids outside of medical settings
- Concurrent abuse of alcohol or illicit drugs
- Repeated requests for dose increases or early refills, despite the presence of adequate analgesia
- Multiple episodes of prescription “loss”
- Repeatedly seeking prescriptions from other clinicians or from emergency rooms without informing prescriber, or after warnings to desist
- Evidence of deterioration in the ability to function at work, in the family or socially, which appears to be related to drug use
- Repeated resistance to changes in therapy despite clear evidence of adverse physical or psychological effects from the drug
- Positive urine drug screen—other substance use

Aberrant Behavior that Requires Attention

- Aggressive complaining about needing more of the drug
- Drug hoarding during periods of reduced symptoms
- Requesting specific drugs
- Openly acquiring similar drugs from other medical sources
- Unsanctioned dose escalation or other noncompliance with therapy on one or two occasions
- Unapproved use of the drug to treat another symptom
- Reporting psychic effects not intended by the clinician
- Resistance to a change in therapy associated with “tolerable” adverse effects, with expressions of anxiety related to the return of severe symptoms
- Missing appointment(s)
- Not following other components of the treatment plan (physical therapy, exercise, etc.)

Adapted from Department of Veterans Affairs and Department of Defense. VA/DoD clinical practice guideline for the management of opioid therapy for chronic pain. Washington, D.C.: Department of Veterans Affairs and Department of Defense; 2003. Available at: <http://www.ihp.gov/nonmedicalprograms/nc4/documents/chronicpainguidelinesva2003.pdf>.

Using Buprenorphine/Naloxone to Manage Opioid Addiction

In 2002, the U.S. Food and Drug Administration (FDA) approved the use of buprenorphine (Subutex) and the combination formulation buprenorphine/naloxone (Suboxone) to manage opioid addiction. Both of these formulations are Schedule III medications. However, most family physicians are required to complete eight hours of training and apply for a waiver before they can prescribe them for opioid addiction.³²

Buprenorphine is a partial μ -opioid receptor agonist; this partial activation makes buprenorphine less likely to be abused by opioid addicts. Naloxone, a μ -opioid receptor antagonist, reverses opioid analgesia and euphoria. Its inclusion with buprenorphine renders the buprenorphine ineffective as an injection.³² Prescribing oral buprenorphine for analgesia is considered an off-label use of the medication in the United States, although it has been widely used as an analgesic in Europe.

The *American Family Physician* article “Managing Opioid Addiction with Buprenorphine” is available online (<http://www.aafp.org/afp/20060501/1573.html>) and provides specific dosing instructions and special considerations for prescribing buprenorphine and buprenorphine/naloxone.

In general, treatment with buprenorphine or buprenorphine/naloxone offers an “exit strategy” for patients whose opioid dependence slips into addiction. Family physicians who are not certified to prescribe buprenorphine may want to work with a physician who is certified and is willing to accept referred patients.

the proper training, prescribing the combination formulation of buprenorphine/naloxone can provide a management alternative for the addicted patient (see the sidebar for more information about using buprenorphine/naloxone).

Conclusion

The appropriate use of opioid therapy to treat chronic nonmalignant pain can ease patients' suffering and improve overall quality of life. While there are certainly obstacles and pitfalls associated with prescribing opioids, many of these potential problems can be avoided by properly assessing and triaging patients who are candidates for opioid therapy; establishing a goal-directed treatment plan;

periodically monitoring patients' adherence and progress toward goals; and thoroughly documenting all decisions and interactions. Family physicians who adopt this systematic approach should be able to successfully treat most patients who have chronic nonmalignant pain in their office and with few truly unmanageable crises.

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