Opioid Analgesia in Chronic Pain

Balancing Benefits and Risk

This activity is based on a teleconference series held in June 2008, with course director Michael R. Clark, MD, MPH.

Special REPORT

Course Director

Michael R. Clark, MD, MPH
Associate Professor and Director
Chronic Pain Treatment Programs
Department of Psychiatry and Behavioral Sciences
The Johns Hopkins Medical Institutions
Baltimore, Maryland

Faculty

Michael Brennan, MD
The Pain Center of Fairfield, Fairfield, Connecticut
Senior Attending Physician, Department of Medicine, Physical Medicine and Rehabilitation
Bridgeport Hospital
Bridgeport, Connecticut

Lynn Webster, MD, FACPM, FASAM
Medical Director
Lifetree Clinical Research and Pain Clinic
Salt Lake City, Utah

Statement of Need

The goal of this initiative is to provide clinicians with current, clinically relevant information on the appropriate and effective use opioid analgesia in patients with chronic noncancer pain (CNCP).

Accreditation Statement

The Johns Hopkins University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Learning Objectives

At the completion of this initiative, participants should be better prepared to:

- Explain the clinical and evidence-based rationale for opioid analgesia in the treatment of CNCP
- Stratify risk and extent of ongoing monitoring for patients receiving opioid pharmacotherapy based on comprehensive initial and continuing assessment and differential diagnosis of aberrant drug-related behaviors
- Describe the pharmacologic properties and expected benefits of emerging opioid formulations designed to resist manipulation and abuse

Presented by The Johns Hopkins University School of Medicine and developed through a strategic educational collaboration with Advanced Strategies in Medicine

Estimated Time to Complete This Activity: 1 hour.

Target Audience

This program is intended for physicians who treat chronic pain, including pain specialists, orthopedic surgeons, neurologists, emergency medicine physicians, rheumatologists, physical medicine and rehabilitation specialists, family practitioners, internists, general practitioners, and oncologists.

Credit Designation

The Johns Hopkins University School of Medicine designates this educational activity for a maximum of 1.0 *AMA PRA Category 1 Credit™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

The Johns Hopkins University School of Medicine takes responsibility for the content, quality, and scientific integrity of this CME activity.

Method of Participation

There are no fees for participating in and receiving credit for this activity. Participants should complete the activity and submit the self-report credit form, multiple-choice post-test answer section, and activity evaluation form on page 8 via mail to CME & Compliance, Advanced Strategies in Medicine, 545 West 45th Street, 7th Floor, New York, NY 10036. A score of at least 70% is required to successfully complete this activity. Certificates will be mailed in approximately 6 to 8 weeks after receipt of mailed submissions and verification of a passing grade. Online participation also is available via CMEZone.com (availability may be delayed from original print date). Enter the project number "SR08023" in the keyword field to access the activity directly. If the post-test is passed, a certificate will be displayed on screen that participants can print and keep for their records. If the post-test is failed, a screen will appear alerting participants of their score and displaying the questions that have been answered incorrectly. One retake is allowed. Credit is available through December 1, 2009.

Faculty Disclosure

As a provider accredited by the ACCME, it is the policy of The Johns Hopkins University School of Medicine to require the disclosure of the existence of any relevant financial interest or any other relationship a faculty member or a provider has with the manufacturer(s) of any commercial product(s) discussed in an educational presentation. The presenting faculty reported the following:

Michael R. Clark, MD, MPH: Eli Lilly and Company, King Pharmaceuticals, Inc., Ligand Pharmaceuticals, Inc., and Pfizer Inc. (speakers' bureaus)

Michael J. Brennan, MD: Alpharma, Cephalon, Inc., Endo Pharmaceuticals, King Pharmaceuticals, Inc., and Purdue (consultant)

Lynn Webster, MD, FACPM, FASAM: Advanced Bionics, Cephalon, Inc., Covidien, Elan Pharmaceuticals, Inc., Elite Pharmaceuticals, Inc., MEDACorp, Medtronic, Inc., (consultant); Abbott Laboratories, Advanced Bionics, Alpharma Pharmaceuticals, Ameritox Ltd, Array BioPharma Inc., AstraZeneca, Boehringer Ingelheim GmbH, Cervelo Pharmaceuticals, CoMentis Inc., Durrect Corporation, Elan Pharmaceuticals, Inc., Elite Pharmaceuticals, Inc., Forest Laboratories, GlaxoSmithKline, Jazz Pharmaceuticals, Inc., King Pharmaceuticals, Inc., Medtronic, Inc., Merck & Co., Inc., Nektar, NeurogesX, PTI, Purdue Pharma, QRX, Respironics, Takeda Pharmaceuticals North America, TorreyPines Therapeutics, Wyeth Pharmaceuticals, ZARS Pharma (grant/research support); Alpharma Pharmaceuticals, Ameritox, Cortex, King Pharma- ceuticals, Inc., Nektar, Nervo, Neuromed, Purdue Pharma LP (advisory boards)

Off-Label Product Discussion

No faculty members or authors have indicated that the monograph will include off-label information.

Disclaimer Statement

The opinions and recommendations expressed by faculty and other experts whose input is included in this program are their own. This enduring material is produced for educational purposes only. Use of The Johns Hopkins University School of Medicine name or Advanced Strategies in Medicine name implies review of educational format, design, and approach. Please review the complete prescribing information for specific drugs or combination of drugs, including indications, contraindications, warnings, and adverse effects before administering pharmacologic therapy to patients.

Date of Release: December 1, 2008

Supported by an educational grant from King Pharmaceuticals, Inc.

Distributed via: PAINMEDICINE NEWS

Date of Expiration: December 1, 2009

CME Zone — Explore the Zone

Introduction

Chronic pain, often defined as pain lasting for more than 6 months and beyond the time required for normal healing, is the main reason patients seek medical attention in the United States.[1,2] Chronic pain also takes a toll on patients' physical, social, and economic well-being. In 2001, the US Congress designated the upcoming decade the "decade of pain control and research," with the goal of increasing awareness and training among physicians and minimizing unnecessary suffering in patients with uncontrolled pain.[3] This designation was followed by a notable increase in the therapeutic use of pain medication—specifically opioid analgesics.[4]

The use of opioids for the treatment of chronic noncancer pain (CNCP) of a variety of etiologies is endorsed by organizations such as the American Academy of Pain Medicine and the American Pain Society,[5] with the acknowledgement that it is associated with certain risks. In fact, as opioid prescribing has increased, so has opioid misuse and abuse (see sidebar, "Using Appropriate Terminology").[6-9] The 2007 National Survey of Drug Use and Health (NSDUH) demonstrated an increase in past-month nonmedical use of pain relievers from 2002 (4.4 million) to 2007 (5.2 million).[10] In fact, the report found that the drug categories with the largest number of past-year initiates (among individuals aged 12 and older) were nonmedically used pain relievers and marijuana—both with 2.1 million new users.

A report from the Drug Abuse Warning Network supported the NSDUH findings; it showed a 153% increase in opioid analgesic-related emergency department (ED) visits from 1995 to 2002, with specific increases of 512%, 176%, 159%, and 116% for oxycodone, methadone, hydrocodone, and morphine, respectively.[11] This increase in opioid misuse and abuse has led to the development of fear among physicians who are facing greater regulatory scrutiny regarding their opioid-prescribing practices, and undertreatment of patients with pain who may benefit from opioid therapy.[12-14]

Using Appropriate Terminology

It is important to recognize the differences among misuse, abuse, and addiction. Although these behaviors all represent inappropriate medication use, they may require different treatment approaches to ensure therapy appropriately and optimize medication outcomes in patients with ongoing chronic pain.

Misuse: Use of a medication for other than prescribed or indicated. Misuse can be unintentional, such as when a patient misunderstands the dosing schedule and takes more medication than prescribed by the physician. Intentional misuse can involve individuals using opioids to cope with psychological pain or stress. In these instances, it is known as drug-seeking behavior.

Abuse: Intermittent or persistent use of a substance for nonmedical purposes, such as alleviating stress or psychological problems.

Addiction: A primary, chronic neurobiologic disease with genetic, psychosocial, and environmental factors. People with the disease of addiction may display impaired control over drug use, compulsive use, continued use despite harm, and craving.

Patients displaying such behaviors can receive opioids but may require close monitoring of counts of the drug dispensed, prescriptions, and frequency of visits.

Role of Opioids in Chronic Pain Management

Effective management of chronic pain is individualized and goal-oriented, with an emphasis on restoring, improving, and maintaining function through analgesia.[15] Studies have shown that a multimodal approach—including psychological support, lifestyle changes, complementary and alternative medicine, physical medicine and rehabilitation, interventional approaches, and/or pharmacotherapy—may be ideal.[16] In addition to opioids, a number of pharmacologic agents are useful in the treatment of patients with chronic pain, including nonsteroidal anti-inflammatory drugs, antidepressants, and anticonvulsants. The literature describing these classes is reviewed elsewhere.[15]

Evidence supports the use of opioids for moderate to severe pain related to a number of CNCP conditions. For example, a meta-analysis of studies with a mean duration of 4 weeks demonstrated significant efficacy for opioids compared with placebo for neuropathic pain.[17] Another study showed significantly decreased pain intensity with extended-release oxymorphone or controlled-release oxycodone compared with placebo over 18 days in patients with chronic low back pain.[18] These and other studies show that opioids are effective during relatively short time periods, but strong evidence supporting the use of long-term opioid therapy is limited.[19]

Proper patient selection is critical to successful opioid-based therapy. It should be informed by a comprehensive assessment of the patient's current condition and comorbidities; physical, psychological, and medical history; relative success with prior treatments; and views regarding opioid use. It also should stratify the patient based on individual risks and balance those risks with the benefits of potential therapies.[20,21] Four questions may help guide the physician considering an opioid trial and help determine whether other modalities have been maximized or should be retried.[21]

1. What is the conventional management of this population and this type of pain?
2. What other treatments have more favorable risk–benefit profiles?
3. What are the current pharmacologic risks related to opioid pharmacotherapy in this patient?
4. Are there concerns about responsible medication use over time?

Risk Assessment and Screening Tools

Risk assessment in patients considered for opioid therapy involves a review of biological, psychological, and social factors associated with the misuse of opioid medications.[22-24] Some experts recommend a Universal Precautions approach (Table),[24] by which all patients undergo risk assessment regardless of initial impressions of their potential risk level. Initially established as an effort to prevent the spread of infectious diseases by applying the same precautions to all patients regardless of known disease status, this approach is used in pain management because it is impossible for physicians to know in advance which patients will misuse, abuse, share, or lose track of their medications. The Universal Precautions approach offers a triage scheme for estimating risk of opioid abuse and recommendations for management and referral. The approach may improve patient care, reduce the stigma associated with possible aberrant drug-taking behaviors, and limit overall risk.

Several self- or clinician-administered screening tools are available to help physicians determine whether a patient is at high, medium, or low risk for opioid abuse.[25-29] The self-administered Opioid Risk Tool (ORT) assesses patients for their personal and family history of substance abuse, age, history of preadolescent sexual abuse (in women), and presence of psychological disease (eg, attention-deficit disorder, obsessive-compulsive disorder, bipolar disorder, depression, schizophrenia).[25] Validation of the ORT has

Table. Universal Precautions in Pain Medicine[24]

1. Diagnosis with appropriate differential
2. Psychological assessment
3. Informed consent
4. Treatment agreements
5. Pain and function assessments
6. Trial of opioid therapy
7. Reassessment of pain and function
8. Regular assessment of the 4 A's: Analgesia, Activities of daily living, Adverse events, Aberrant drug-taking behavior
9. Periodic review of diagnosis and comorbidities
10. Documentation

demonstrated that 91% of patients stratified to the high-risk category and only 6% of those in the low-risk category will display aberrant drug-taking behavior. The Screener and Opioid Assessment for Patients with Pain-Revised Version (SOAPP-R) is self-administered by patients who are being considered for long-term opioid therapy.[27] It is designed to help predict which patients will exhibit aberrant medication-related behaviors and is less susceptible to overt deception than the previous version. Creation of the SOAPP-R involved concept mapping of 142 items covering 8 domains: antisocial behaviors/history, substance abuse history, medication-related behaviors, doctor– patient relationship, psychiatric history, emotional attachment to pain medications, personal care and lifestyle, and psychosocial problems. Validation of this screening tool revealed that 90% of patients stratified into the high-risk category eventually display aberrant drug-taking behaviors. These tools should be used within the context of an overall evaluation of risk.

Opioid Therapy: Structure, Selection, And Titration

Most patients are stratified as low risk for abuse,[30] and their opioid treatment can be managed adequately by a primary care physician (PCP). Others who are classified as moderate or high risk require more stringent monitoring[24] via frequent office visits, small prescription volumes, pill counts, and periodic urine drug testing (UDT). These individuals also may benefit from referral to or comanagement with an addiction and/or pain specialist. For patients with a current or past substance abuse problem, the possibility for opioid abuse often leads physicians to consider nonopioid or nonpharmacologic treatments.

A certain level of structure is recommended for all patients receiving opioid therapy. For example, prescriptions should be filled at one pharmacy only and should be stored securely to avoid access by others. These and other treatment parameters can be outlined clearly in an opioid treatment agreement (OTA) to which patient and physician agree. An OTA states that the initiation of opioid therapy is a joint decision made by both parties, acknowledges the expected risks and benefits of these drugs, formalizes the structure of opioid therapy, and emphasizes responsibilities to be shared throughout the course of treatment.[31]

Once a structure has been established, the physician has a variety of opioid formulations from which to choose, including long-acting opioids (LAOs), which generally are dosed 1 to 3 times daily for persistent, around-the-clock pain; and short-acting opioids (SAOs), which usually are given up to 4 times daily as needed (and include a subgroup of rapid-onset fentanyl formulations indicated specifically for brief, intense episodes of breakthrough cancer-related pain). Each type of medication has advantages;

Interpreting UDT Results

Careful interpretation of results including the detection of false-positives and false-negatives is required for UDT to be a useful component of patient monitoring. A false-negative result may be caused by a dilute urine sample, abnormally rapid drug metabolism in a patient, or the inability of a laboratory to detect certain drugs. False-positive results likely are due to cross-reactivity between legitimately prescribed, over-the-counter, or herbal agents that the patient might be taking at the same time. Accurate identification of false-positives and false-negatives requires consideration of all available information from the patient's history and physical examination for issues that might relate to the laboratory, clinician, or patient. UDT results accurately should be flagged.

Many physicians have difficulty interpreting a UDT correctly. In a recent study, a series of 6 open-book, best-answer, multiple-choice questions and 1 yes or no question about UDT interpretation were administered to physicians who use UDT to monitor patients taking opioids for chronic pain. None of the physicians answered all the questions correctly, and only 30% answered more than half of the questions correctly.[1] The questions focused on the following issues:

- UDT results for patients taking only codeine may show codeine and/or morphine (codeine is metabolized partially to morphine).
- UDT results for patients taking only morphine will show only morphine.
- UDT results for patients taking only hydromorphone will show only morphine (hydromorphone usually is not detected because of its short half-life and is metabolized partially to morphine).
- UDT results for patients taking a moderate amount of oxycodone may show codeine and/or morphine.
- UDT results for patients exposed to second-hand marijuana smoke will not show tetrahydrocannabinol (federally prohibited substance).
- UDT results for patients with unusually rapid metabolism may show as false-negative for opioids.
- UDT results for patients taking hydromorphone may show as false-negative for opioids (gas chromatography–mass spectrometry should be used to detect this partially synthesized opioid).

some studies suggest that patients receiving an LAO report enhanced pain control and reduced pain-related disability related to anxiety, depression, or sleep disturbance,[32,33] whereas others hypothesize that less frequent dosing with longer-acting formulations may reduce "clock watching"—anxiety that may develop when patients anticipate their next drug dose as analgesia begins to dwindle. Overall, however, there is limited evidence demonstrating that either SAOs or LAOs are better suited for the treatment of persistent pain.[34-37]

To determine the appropriate dosage, physicians often initiate an SAO, titrate to achieve an adequate balance between analgesia and side effects, and then decide whether to switch to an LAO depending on patient preference and pain profile. This is important especially in opioid-naïve patients in whom the adverse effects are unknown. Some physicians feel confident that titration with an

LAO is more advantageous, particularly in selected patients with experience taking opioids.

Ongoing Monitoring of Opioid Therapy: Measuring Benefits and Risks

Over time, ongoing assessment of patients prescribed opioid therapy is critical as it may reveal loss of efficacy, intolerable side effects, or the development of aberrant medication-related behaviors. Careful, individualized interpretation and response to these events will help the physician adjust dosages or change medications as necessary. Reassessment may be facilitated using the 4 A's: Analgesia, Adverse effects, Activities of daily living, and Aberrant drug-taking.[38,39] Monitoring these 4 domains reminds the physician that treatment involves more than just decreasing pain intensity; it should manage side effects, stabilize and improve psychosocial functioning, and provide an approach to assess and control possible misuse.

As occurs with other drug classes, long-term administration of opioids may result in tolerance—defined as diminished antinociceptive or analgesic effect due to chronic medication exposure—and thus a need for an increased dose to maintain analgesia. Some patients may find the side effects associated with higher doses intolerable[60]; in these cases, opioid rotation (switching to a different opioid) may be necessary. For many physicians and patients, opioid rotation leads to re-established control over pain and/or adverse effects associated with a particular medication. The mechanism by which opioid rotation is effective is unclear, but studies point to the pharmacogenetic, pharmacokinetic, and pharmacodynamic characteristics of opioids as its basis.[40-42] Moreover, recent research has identified genetic variability in enzymes, receptors, and transporters that may affect the potency and metabolism of specific opioids in individual patients.[43,44]

The intensity of behavioral monitoring for patients prescribed long-term opioid therapy should be adjusted based on the individualized risk stratification performed at treatment onset and changes observed during follow-up. For example, a patient stratified initially as moderate risk may begin to display behaviors consistent with higher risk and thus may warrant an increase in the structural stringency of his or her pharmacologic regimen. Careful interpretation of such behaviors is key to implementing the proper therapeutic solutions. Some actions—such as forging or stealing prescriptions, concurrent abuse of illicit drugs, and multiple unsanctioned dose escalations—are thought to be more predictive of opioid misuse or abuse, whereas others—such as requests for specific drugs or unapproved use of the drug to treat another symptom—are considered less so.[45]

The Role of Urine Drug Testing

In addition to observation of patient actions, UDT should be considered during initial assessment and ongoing monitoring of patients who are treated with opioid therapy for chronic pain.[46,47] Studies show that UDT is more effective in identifying nonadherent patients than behavior monitoring or self-reporting alone.[48-50] In addition, periodic unannounced UDT may deter illegal drug use or prescription drug abuse, and it can provide documentation to regulatory authorities should prescribing practices be questioned.[51]

Despite these advantages, UDT is not used often in practice. A recent review of medical records from 12 family care practices found that only 8% of PCPs used UDT as a component of their regular assessment and ongoing monitoring.[52]

Interpreting UDT results requires caution (see sidebar, "Interpreting UDT Results," page 3).[53-55] Many types of UDT were intended for or adapted from workplace requirements and have not been optimized for monitoring patients undergoing long-term opioid therapy[51,57]; workplace testing generally is designed to identify heroin, morphine, or codeine, whereas numerous other opioids are used in the pain management setting, including hydrocodone, hydromorphone, and oxycodone. Therefore, it is necessary to ensure that the UDT laboratory tests the sample for the appropriate drugs. Different techniques are used in UDT, each with its own advantages and disadvantages. For example, most immunoassay screening methods are relatively rapid and cost-effective but may only be able to detect the presence of a drug class, not a specific drug.[57] Alternatively, gas chromatography/mass spectrometry is highly specific and sensitive and can identify molecular structures, metabolites, and the amount present; however, this technique can be expensive.[51] Knowledge of different testing laboratories' limits, how to read laboratory results, and the technology involved in sample testing will yield a more accurate interpretation of results for each patient.

Improving Outcomes Through Multidisciplinary Care

The Opioid Renewal Clinic, a treatment program carried out at an urban, academic Veterans Affairs Medical Center (VAMC), demonstrated that proper PCP training and support can lead to increased treatment success in patients stratified to higher risk categories. The goals of the program were to provide proper patient treatment; improve monitoring, documentation, and PCP confidence when prescribing opioids; reduce prescribing of sustained-action oxycodone; and lower overall costs of care by decreasing misuse or overuse of resources.[58] To achieve these goals, a nurse practitioner, a clinical pharmacist, and a multidisciplinary team of consultants supported PCPs in managing patients who were undergoing opioid treatment for chronic pain. Two years later, PCPs demonstrated increased confidence in opioid prescribing, use of OTAs, and UDT. Furthermore, overall spending for sustained-action oxycodone significantly decreased from $129,793 to $5,236 and ED visits and unscheduled office visits declined an average of 72.7% and 59.6% per patient, respectively. Many patient-specific problems also improved. Of those who entered the program, 51% had documented aberrant drug-taking behaviors. During the course of the treatment, 45% of the problematic patients were adherent to the OTA and resolved their behavior, 38% self-discharged, 13% were referred for addiction treatment, and 4% with UDT consistently negative for the prescribed opioid were titrated off opioids. This treatment approach demonstrated that a structured program for opioid management in VAMC patients with chronic pain could be implemented successfully.

Advances in Opioid Formulations

In recent years, research has been under way to develop opioid agents that combine analgesic efficacy with reduced risk for abuse. These drugs generally involve a physical or pharmacologic barrier to block unintended use.[59] They have been described as "abuse-resistant" and "abuse-deterrent," respectively, but these terms have not been approved by the FDA for use in product information, and whether these formulas actually reduce misuse and abuse requires large-scale epidemiologic study.

A new drug application (NDA) has been submitted for a long-acting oxycodone formulated in a matrix that resists mechanical manipulation (eg, crushing, chewing, snorting, injecting) as well as dose dumping in ethanol.[60-62] Data recently presented at the 12th World Congress of the International Association for the Study of Pain in Glasgow, Scotland, showed that ingestion of the drug along with simulated binge-drinking did not defeat the controlled-release property.[63] A 12-week, Phase III clinical study demonstrated that the drug is effective as a twice-daily analgesic in patients with osteoarthritis of the hip or knee.[64] An investigational form of tramadol in a viscous

gel also is being tested to determine whether it can withstand attempts at extraction by physical or chemical means.[65]

An NDA has been submitted for a formulation of extended-release morphine sulfate with sequestered naltrexone, an opioid antagonist.[59] When taken as indicated, the drug should travel through the gastrointestinal tract releasing the analgesic medication and not the naltrexone antagonist. If crushed to alter the delivery route, the naltrexone is released to block both the euphoric and analgesic effects of the drug.

A short-acting oxycodone formulation with multiple physical and pharmacologic properties that attempt to reduce its abuse liability also is in late-stage development. It contains subtherapeutic amounts of niacin that should not affect patients taking the recommended dose but should cause transient unpleasant effects, such as flushing, itching, headache, and a general feeling of discomfort, when consumed orally in excess.[66] In addition, this drug formulation contains a surfactant to cause nasal irritation if the user attempts to snort it, and a matrix that forms a viscous gel in aqueous solution to prevent injecting.

Other formulations being considered or developed include prodrugs that become active only when ingested orally and numerous drugs with properties similar to the above-described formulations.[59]

Exit Strategies

Several situations may warrant discontinuation of opioid therapy. Some patients may not benefit from opioids despite attempts to adjust doses, manage side effects, or rotate to alternative opioids; and others may fail repeatedly to adhere to the treatment plan. In these circumstances, an exit strategy may be necessary (Figure).[20] Such a strategy should be discussed and individualized prior to initiation of an opioid trial, so the patient does not feel abandoned should opioids not be appropriate.[19] If an exit strategy is enacted, the physician should stress that stopping opioid therapy does not mean giving up on treatment. Instead, patients with ongoing chronic pain conditions may be managed using different pharmacologic and nonpharmacologic approaches or an appropriate referral.

Although no single exit strategy can be applied to all patients, the unifying factor involves tapering the opioid to prevent withdrawal while continuing pain management. For patients who have addiction problems, referral to or comanagement with an addiction specialist is warranted. For who do not have addiction problem and are able to discontinue opioid therapy on an outpatient basis, gradual tapering can be conducted successfully over a 1-month period. Often, 50% of an opioid dose can be decreased in the first 1 or 2 days, after which tapering should be slowed. If patients display unwillingness to cooperate with outpatient tapering, they should be referred for inpatient detoxification and given a sufficient amount of medication until they are admitted. Inpatient programs use medications such as methadone and buprenorphine to ease withdrawal symptoms in a secure, supportive environment.

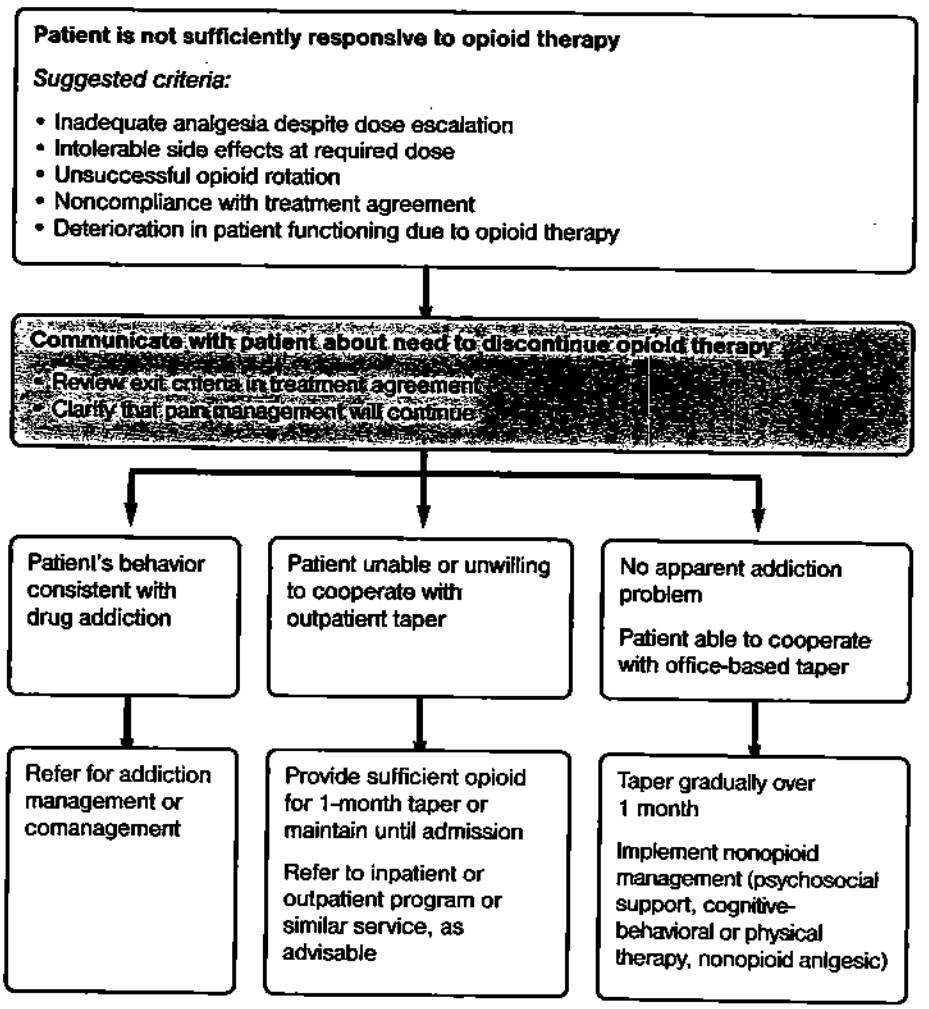

Figure. Opioid exit strategies.[20]

Conclusion

Opioid analgesics are effective for a variety of chronic pain conditions, but their long-term use remains a contentious issue because of their potential for misuse and abuse. An understanding of the proper techniques for initiating, monitoring, and discontinuing opioid analgesic therapy may limit the extent of such abuse. Proper initial patient assessment and risk stratification are the first steps toward identifying a legitimate need for opioid therapy and determining the requisite degree of individualized structure. Patients undergoing opioid therapy also should be monitored continually through routine assessment of analgesia, functioning, side effects, and aberrant behaviors. Adhering to these fundamental treatment approaches can provide a foundation for minimizing abuse of opioid analgesics in patients with chronic pain conditions. Finally, emerging formulations may help reduce prescription opioid abuse and provide added comfort in prescribing in the future.

References

1. US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics. *Health, United States, 2006 with Chartbook on Trends in the Health of Americans*. Rockville, MD: US Department of Health and Human Services; 2006:116-124.
2. International Association for the Study of Pain. How Prevalent is Chronic Pain? *Pain: Clinical Updates*. 2003;11(2):1-4.
3. Nelson R. Decade of pain control and research gets into gear in USA. *Lancet*. 2003;362(9390):1129.
4. Manchikanti L, Singh A. Therapeutic opioids: a ten-year perspective on the complexities and complications of the escalating use, abuse, and nonmedical use of opioids. *Pain Physician*. 2008;11(2 suppl):S63-88.
5. The use of opioids for the treatment of chronic pain. A consensus statement from American Academy of Pain Medicine and American Pain Society. *Clin J Pain*. 1997;13(1):6-8.
6. Katz NP, Adams EH, Chilcoat H, et al. Challenges in the development of prescription opioid abuse-deterrent formulations. *Clin J Pain*. 2007;23(8):648-660.
7. Kirsh KL, Jass C, Bennett DS, Hagen JE, Passik SD. Initial development of a survey tool to detect issues of chemical coping in chronic pain patients. *Palliat Support Care*. 2007;5(3):219-226.
8. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Text Revision. Washington, DC: American Psychiatric Association; 2000.
9. US Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Office of Applied Studies. *The National Survey on Drug Use and Health: The NSDUH Report*. Rockville, MD: US Department of Health and Human Services; 2007.
10. US Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Office of Applied Studies. *Results from the 2007 National Survey on Drug Use and Health: National Findings*. Rockville, MD: US Department of Health and Human Services; 2008.
11. US Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Office of Applied Studies. *Drug Abuse Warning Network: The DAWN report: Narcotic Analgesics, 2002 Update*. Rockville, MD: US Department of Health and Human Services; 2004:1-4.
12. Hoffmann DE, Tarzian AJ. Achieving the right balance in oversight of physician opioid prescribing for pain: the role of state medical boards. *J Law Med Ethics*. 2003;31(1):21-40.
13. Nwokeji ED, Rascati KL, Brown CM, Eisenberg A. Influences of attitudes on family physicians' willingness to prescribe long-acting opioid analgesics for patients with chronic nonmalignant pain. *Clin Ther*. 2007;29(suppl):2589-2602.
14. Weinstein SM, Laux LF, Thornby JI, et al. Physicians' attitudes toward pain and the use of opioid analgesics: results of a survey from the Texas Cancer Pain Initiative. *South Med J*. 2000;93(5):479-487.
15. McCarberg B. Contemporary management of chronic pain disorders. *J Fam Pract*. 2004;53(suppl 10):S11-S22.
16. Fine PG, Miaskowski C, Paice JA. Meeting the challenges in cancer pain management. *J Support Oncol*. 2004;2(6 suppl 4):5-22.
17. Eisenberg E, McNicol ED, Carr DB. Efficacy and safety of opioid agonists in the treatment of neuropathic pain of nonmalignant origin: systematic review and meta-analysis of randomized controlled trials. *JAMA*. 2005;293(24):3043-3052.
18. Hale ME, Dvergsten C, Gimbel J. Efficacy and safety of oxymorphone extended release in chronic low back pain: results of a randomized, double-blind, placebo- and active-controlled phase III study. *J Pain*. 2005;6(1):21-28.
19. Noble M, Tregear SJ, Treadwell JR, Schoelles K. Long-term opioid therapy for chronic noncancer pain: a systematic review and meta-analysis of efficacy and safety. *J Pain Symptom Manage*. 2008;35(2):214-228.
20. Katz N. *Patient Level Opioid Risk Management: a Supplement to the PainEDU.org Manual*. Newton, MA: Inflexion, Inc; 2007.
21. Fine PG, portenoy RK. *A Clinical Guide to Opioid Analgesia*. 2nd ed. New York: Vendome Group, LLC; 2007.
22. Katz NP, Adams EH, Benneyan JC, et al. Foundations of opioid risk management. *Clin J Pain*. 2007;23(2):103-116.
23. Manchikanti L, Giordano J, Boswell MV, Fellows B, Manchukonda R, Pampati V. Psychological factors as predictors of opioid abuse and illicit drug use in chronic pain patients. *J Opioid Manag*. 2007;3(2):89-100.
24. 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.
25. 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.
26. Butler SF, Budman SH, Fernandez KC, et al. Development and validation of the Current Opioid Misuse Measure. *Pain*. 2007;130(1-2):144-156.
27. Butler SF, Fernandez K, Benoit C, Budman SH, Jamison RN. Validation of the Revised Screener and Opioid Assessment for Patients With Pain (SOAPP-R). *J Pain*. 2008;9(4):360-372.
28. Brennan MJ. DIRE: a tool to assess risks of maintaining opioid treatment. *J Pain*. 2007;8(2):185, author reply 186.
29. Coambs RB, & Jarry, J. L. The SISAP: a new screening instrument for identifying potential opioid abusers in the management of chronic nonmalignant pain in general medical practice. *Pain Res Manag*. 1996;1(3):155-162.
30. Passik S, Kirsh K, Whitcomb L, et al. Monitoring outcomes during long-term opioid therapy for noncancer pain: Results with the Pain Assessment and Documentation Tool. *J Opioid Manag*. 2005;1(5):257-266.
31. Burchman SL, Pagel PS. Implementation of a formal treatment agreement for outpatient management of chronic nonmalignant pain with opioid analgesics. *J Pain Symptom Manage*. 1995;10(7):556-563.
32. Portenoy RK, Sciberras A, Eliot L, Loewen G, Butler J, Devane J. Steady-state pharmacokinetic comparison of a new, extended-release, once-daily morphine formulation, Avinza, and a twice-daily controlled-release morphine formulation in patients with chronic moderate-to-severe pain. *J Pain Symptom Manage*. 2002;23(4):292-300.
33. Pujol LM KN, Zacharoff KL. *The PainEdu.org Manual*: A pocket guide to pain management. 3rd Edition; Newton MA: Inflexion, Inc.; 2007.
34. Jamison RN, Raymond SA, Slawsby EA, Nedeljkovic SS, Katz NP. Opioid therapy for chronic noncancer back pain. A randomized prospective study. *Spine*. 1998;23(23):2591-2600.
35. Caldwell JR, Hale ME, Boyd RE, et al. Treatment of osteoarthritis pain with controlled release oxycodone or fixed combination oxycodone plus acetaminophen added to nonsteroidal antiinflammatory drugs: a double blind, randomized, multicenter, placebo controlled trial. *J Rheumatol*. 1999;26(4):862-869.
36. Hale ME, Fleischmann R, Salzman R, et al. Efficacy and safety of controlled-release versus immediate-release oxycodone: randomized, double-blind evaluation in patients with chronic back pain. *Clin J Pain*. 1999;15(3):179-183.
37. Salzman RT, Roberts MS, Wild J, Fabian C, Reder RF, Goldenheim PD. Can a controlled-release oral dose form of oxycodone be used as readily as an immediate-release form for the purpose of titrating to stable pain control? *J Pain Symptom Manage*. 1999;18(4):271-279.
38. Passik SD, Kirsh KL. Managing pain in patients with aberrant drug-taking behaviors. *J Support Oncol*. 2005;3(1):83-86.
39. Passik SD, Kirsh KL, Whitcomb L, et al. A new tool to assess and document pain outcomes in chronic pain patients receiving opioid therapy. *Clin Ther*. 2004;26(4):552-561.
40. Pasternak G. Deciphering the efficacy of opioid rotation. *Pain Management Today*. 2006;6(2):1,10-11.
41. Indelicato RA, Portenoy RK. Opioid rotation in the management of refractory cancer pain. *J Clin Oncol*. 2002;20(1):348-352.
42. Thomsen AB, Becker N, Eriksen J. Opioid rotation in chronic non-malignant pain patients. A retrospective study. *Acta Anaesthesiol Scand*. 1999;43(9):918-923.
43. Foster A, Mobley E, Wang Z. Complicated pain management in a CYP450 2D6 poor metabolizer. *Pain Pract*. 2007;7(4):352-356.
44. Kadiev E, Patel V, Rad P, et al. Role of pharmacogenetics in variable response to drugs: focus on opioids. *Expert Opin Drug Metab Toxicol*. 2008;4(1):77-91.
45. Passik SD, Kirsh KL, Donaghy KB, Portenoy RK. Pain and aberrant drug-related behaviors in medically ill patients with and without histories of substance abuse. *Clin J Pain*. 2006;22(2):173-181.
46. Fleming MF, Balousek SL, Klessig CL, Mundt MP, Brown DD. Substance use disorders in a primary care sample receiving daily opioid therapy. *J Pain*. 2007;8(7):573-582.
47. Bhamb B, Brown D, Hariharan J, Anderson J, Balousek S, Fleming MF. Survey of select practice behaviors by primary care physicians on the use of opioids for chronic pain. *Curr Med Res Opin*. 2006;22(9):1859-1865.
48. Wasan AD, Butler SF, Budman SH, Benoit C, Fernandez K, Jamison RN. Psychiatric history and psychologic adjustment as risk factors for aberrant drug-related behavior among patients with chronic pain. *Clin J Pain*. 2007;23(4):307-315.