Clinical Policy: Critical Issues in the Prescribing of Opioids for Adult Patients in the Emergency Department

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ABSTRACT

This clinical policy deals with critical issues in prescribing of opioids for adult patients treated in the emergency department (ED). This guideline is the result of the efforts of the American College of Emergency Physicians, in consultation with the Centers for Disease Control and Prevention, and the Food and Drug Administration. The critical questions addressed in this clinical policy are: (1) In the adult ED patient with noncancer pain for whom opioid prescriptions are considered, what is the utility of state prescription drug monitoring programs in identifying patients who are at high risk for opioid abuse? (2) In the adult ED patient with acute low back pain, are prescriptions for opioids more effective during the acute phase than other medications? (3) In the adult ED patient for whom opioid prescription is considered appropriate for treatment of new-onset acute pain, are short-acting schedule II opioids more effective than short-acting schedule III opioids? (4) In the adult ED patient with an acute exacerbation of noncancer chronic pain, do the benefits of prescribing opioids on discharge from the ED outweigh the potential harms?

INTRODUCTION

Pain is a major symptom of many patients presenting to the emergency department (ED), with up to 42% of ED visits being related to painful conditions.[1] Pain management has received increased emphasis in the past decade, including The Joint Commission's focus on patient analgesia[2] and increasing institutional emphasis placed on patient satisfaction surveys covering pain management. Much literature, including the most recent Institute of Medicine report on this topic, has stressed that health care providers have not done as well as possible in the area of pain management.[3] A possible unintended consequence of these efforts is the increase in prescription drug abuse, especially opioid abuse, the fastest-growing drug abuse problem in the United States.[4]

As part of this issue, there has been a startling increase in unintentional drug overdoses and related deaths since the late 1990s.[5,6] Reported overdose deaths involving opioid analgesics increased from 4,030 in 1999 to 14,800 in 2008.[7,8] Data from 2008 reveal that drug overdoses were the second leading cause of injury death in the United States, after motor vehicle crashes.[9] Currently, deaths from opioid analgesics are significantly greater in number than those from cocaine and heroin combined.[8]

The efforts of clinicians to improve their treatment of pain, along with pharmaceutical industry marketing, have been factors in contributing to a significant increase in the sale and distribution of opioids in the United States. For example, the sales of opioid analgesics to hospitals, pharmacies, and practitioners quadrupled between 1999 and 2010.[8] Drug sales and distribution data of opioids show an increase from 180 mg morphine equivalents per person in the United States in 1997 to 710 mg per person in 2010.[8,10] This is the equivalent of 7.1 kg of opioid medication per 10,000 population, or enough to supply every American adult with 5 mg of hydrocodone every 4 hours for a month.[8]

The dilemma of treating pain appropriately while avoiding adverse events is further complicated by insufficient data supporting the long-term use of opioids in the treatment of chronic noncancer pain. Although selective use of opioids in the treatment of acute pain is traditionally accepted, the treatment of chronic noncancer pain is more complex. Many authors have begun to question the routine long-term use of opioids for the treatment of chronic noncancer pain.[11-13] Multiple practice guidelines have been developed to address this issue.[14-19] However, most recommendations in this area are of a consensus nature, being based on experiential or low-quality evidence.

Data from 2009 show that there were more than 201.9 million opioid prescriptions dispensed in the United States during that year.[20] It is difficult to obtain reliable data concerning the degree to which this is an emergency medicine issue, but during 2009, in the 10- to 19-year-old and 20- to 29-year-old patient groups, emergency medicine ranked third among all specialties in terms of number of opioid prescriptions, writing approximately 12% of the total prescriptions in each age group. In the 30- to 39-year-old group, emergency medicine ranked fourth.[20] Although these data do not deal with total doses dispensed by specialty, it is commonly postulated that the population served in EDs as a whole is at high risk for opioid abuse.[21]

The significant increase in opioid-related deaths has raised the concern of many.[5,6,8] This problem has also been observed in the pediatric population.[22-24] Action at the national level includes the recent proposal from the Food and Drug Administration for the establishment of physician education programs for the prescribing of long-acting and extended-release opioids as part of their national opioid risk evaluation and mitigation strategy (the REMS program).[25] State efforts to address this issue have included the development of statewide opioid prescribing guidelines, such as those developed by the Utah Department of Health[17] and statewide ED opioid prescribing guidelines, such as those developed in Washington State by the Washington chapter of the American College of Emergency Physicians (ACEP) working with other state organizations.[16] Some individual EDs and emergency physician groups have also promulgated opioid prescribing guidelines. Some of these policies also deal with the necessity of patient education about the safe use and proper disposal of opioid medications. Early data indicate that, in some cases, these guidelines may decrease prescription opioid overdose.[26] Anecdotal experience suggests that public policies such as these may change patient perceptions of appropriate prescribing and mitigate complaints arising from more stringent prescribing practices. ACEP has approved related policy statements about optimizing the treatment of pain in patients with acute presentations and the implementation of electronic prescription drug monitoring programs.[27,28]

This clinical policy addresses several issues believed to be important in the prescribing of opioids by emergency physicians for adult patients treated and released from the ED for whom opioids may be an appropriate treatment modality. Although relieving pain and reducing suffering are primary emergency physician responsibilities, there is a concurrent duty to limit the personal and societal harm that can result from prescription drug misuse and abuse. Because long-acting or extended-release opioids are not indicated for the treatment of acute pain, the aim of this clinical policy is to provide evidence-based recommendations for prescribing short-acting opioids for adult ED patients with painful acute or chronic conditions while attempting to address the increasing frequency of adverse events, abuse, and overdose of prescribed opioid analgesics.

METHODOLOGY

This clinical policy was created after careful review and critical analysis of the medical literature. The critical questions were formulated in the PICO (patient, intervention, comparison, outcome)[29] format to strengthen the clarity and scientific rigor of the questions. Searches of MEDLINE, MEDLINE InProcess, and the Cochrane Library were performed. All searches were limited to English-language sources, human studies, adults, and years 2000 to 2011. Specific key words/phrases and years used in the searches are identified under each critical question. In addition, relevant articles from the bibliographies of included studies and more recent articles identified by committee members were included.

This policy is a product of the ACEP clinical policy development process, including expert review, and is based on the literature; when literature was not available, consensus of panel members was used. Expert review comments were received from emergency physicians, toxicologists, pain and addiction medicine specialists, pharmacologists, occupational medicine specialists, and individual members of the American Academy of Clinical Toxicology, American Academy of Family Physicians, American Academy of Pain Medicine, American Chronic Pain Association, American College of Occupational and Environmental Medicine, American College of Osteopathic Emergency Physicians, American College of Physicians, American Pain Society, American Society of Health-System Pharmacists, American Society of Interventional Pain Physicians, Emergency Medicine Resident's Association, and Emergency Nurses Association. Their responses were used to further refine and enhance this policy; however, their responses do not imply endorsement of this clinical policy. Clinical policies are scheduled for revision every 3 years; however, interim reviews are conducted when technology or the practice environment changes significantly. The Centers for Disease Control and Prevention was the funding source for this clinical policy.

All articles used in the formulation of this clinical policy were graded by at least 2 subcommittee members for quality and strength of evidence. The articles were classified into 3 classes of evidence on the basis of the design of the study, with design 1 representing the strongest evidence and design 3 representing the weakest evidence for therapeutic, diagnostic, and prognostic studies, respectively (Appendix A). Articles were then graded on dimensions related to the study's methodological features: blinded versus nonblinded outcome assessment, blinded or randomized allocation, direct or indirect outcome measures (reliability and validity), biases (eg, selection, detection, transfer), external validity (ie, generalizability), and sufficient sample size. Articles received a final grade (Class I, II, III) on the basis of a predetermined formula, taking into account the design and study quality (Appendix B). Articles with fatal flaws or that were not relevant to the critical question were given an "X" grade and were not used in formulating recommendations for this policy. Evidence grading was done with respect to the specific data being extracted and the specific critical question being reviewed. Thus, the level of evidence for any one study may have varied according to the question, and it is possible for a single article to receive different levels of grading as different critical questions were answered. Question-specific level of evidence grading may be found in the Evidentiary Table included at the end of this policy. Evidence grading sheets may be viewed at http://www.acep.org/clinicalpolicies/?pg=1.

Clinical findings and strength of recommendations about patient management were then made according to the following criteria:

Level A recommendations. Generally accepted principles for patient management that reflect a high degree of clinical certainty (ie, based on strength of evidence Class I or overwhelming evidence from strength of evidence Class II studies that directly address all of the issues).

Level B recommendations. Recommendations for patient management that may identify a particular strategy or range of management strategies that reflect moderate clinical certainty (ie, based on strength of evidence Class II studies that directly address the issue, decision analysis that directly addresses the issue, or strong consensus of strength of evidence Class III studies).

Level C recommendations. Other strategies for patient management that are based on Class III studies, or in the absence of any adequate published literature, based on panel consensus.

There are certain circumstances in which the recommendations stemming from a body of evidence should not be rated as highly as the individual studies on which they are based. Factors such as heterogeneity of results, uncertainty about effect magnitude and consequences, and publication bias, among others, might lead to such a downgrading of recommendations.

This policy is not intended to be a complete manual on the evaluation and management of adult ED patients with painful conditions where prescriptions for opioids are being considered, but rather is a focused examination of critical issues that have

particular relevance to the current practice of emergency medicine.

The goal of the ACEP Opioid Guideline Panel is to provide an evidence-based recommendation when the medical literature provides enough quality information to answer a critical question. When the medical literature does not contain enough quality information to answer a critical question, the members of the ACEP Opioid Guideline Panel believe that it is equally important to alert emergency physicians to this fact.

Recommendations offered in this policy are not intended to represent the only management options that the emergency physician should consider. ACEP clearly recognizes the importance of the individual physician's judgment. Rather, this guideline defines for the physician those strategies for which medical literature exists to provide support for answers to the critical questions addressed in this policy.

Scope of Application. This guideline is intended for physicians working in hospital-based EDs.

Inclusion Criteria. This guideline is intended for adult patients presenting to the ED with acute noncancer pain or an acute exacerbation of chronic noncancer pain.

Exclusion Criteria. This guideline is not intended to address the long-term care of patients with cancer or chronic noncancer pain.

CRITICAL QUESTIONS

1. In the adult ED patient with noncancer pain for whom opioid prescriptions are considered, what is the utility of state prescription drug monitoring programs in identifying patients who are at high risk for opioid abuse?

Recommendations

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations. The use of a state prescription monitoring program may help identify patients who are at high risk for prescription opioid diversion or doctor shopping.

Key words/phrases for literature searches: opioid, drug prescriptions, drug monitoring, drug utilization review, substance abuse detection, drug-seeking behavior, drug and narcotic control, substance-related disorders, physician's practice patterns, program evaluation, emergency service, and variations and combinations of the key words/phrases with exclusion of cancer.

Emergency physicians must balance oligoanalgesia (undertreatment or ineffectual treatment of pain) with concerns about drug diversion* and doctor shopping.†[30-33] Therefore, the development of mechanisms to address these issues is justified. The expanded use of prescription drug monitoring programs to curb prescription opioid misuse was recommended in the 2011 Prescription Drug Abuse Prevention Plan released by the White House Office of National Drug Control Policy.[34] Prescription drug monitoring programs are state-based monitoring programs for certain controlled substances that are prescribed by licensed practitioners and dispensed by pharmacies. Although existing in various forms for more than 3 decades, the first effort to standardize prescription drug monitoring practice was the passage in 2005 of the National All Schedules Prescription Electronic Reporting Act (NASPER). Unfortunately, this federal legislative mandate that intended to harmonize prescription drug monitoring programs across the various states has yet to be fully funded.

Prescription drug monitoring programs ideally serve multiple functions, including identifying patients who engage in doctor shopping, and patients, providers, or pharmacies who engage in diversion of controlled substances and providing information about prescribing trends for surveillance and evaluation purposes. Such information may serve to benefit the patients, the health care system, epidemiologists, policymakers, regulatory agencies, and law enforcement.[35] Certain large health care systems, particularly closed prescribing systems such as the Veterans Administration and health maintenance organizations, maintain databases that allow prescribers to view recent prescriptions of enrolled clients or patients. Forty-one states have operational prescription drug monitoring programs of various complexity and capability, with an additional 7 states having prescription drug monitoring program legislation in place but with programs that are not yet operational. [36] Most states allow health care providers and pharmacists to access the programs for patients under their care. Other groups such as law enforcement and regulatory boards may also have access. One program tracks only schedule II drug prescriptions, whereas most track drug prescriptions of schedule II to IV or II to V drugs.

Despite prescription drug monitoring programs providing an intuitive perception of benefit for the medical community, there are limited data to indicate any benefit of these programs for improving patient outcomes or reducing the misuse of prescription drugs.[37] In part, this relates to the limited optimization of and standardization between the programs and the lack of a mechanism to allow interstate communication.[35]

*Drug diversion: The diversion of drugs for nonmedical use through routes that do not involve the direct prescription of the drug by a provider. Diverted drugs might be provided by family or friends, purchased on the street market, or obtained through fraudulent prescription. Epidemiologic data suggest that most opioids used nonmedically are obtained through these means.

†Doctor shopping: The practice of obtaining prescriptions for controlled substances from multiple providers, which is regarded as a possible indication of abuse or diversion. There is no rigorous definition, and various authors have defined it in different ways, from 2 or more prescribers within 30 days, greater than 4 during 1 year, and greater than 5 during 1 year.[30-32] It has also been defined as the amount of drug obtained through doctor shopping compared with the amount intended to be prescribed.[33] The use of "pill mills," in which a prescriber provides ready access to prescriptions or pills, can be considered a form of doctor shopping.

One study has demonstrated that compared with states without a prescription monitoring program, those with such a program had a slower rate of increase in opioid misuse.[38]

In an attempt to quantify the effect of a prescription drug monitoring program, Baehren et al[39] conducted a prospective study (Class III) of 18 providers who cared for a convenience sample of adult patients with pain in a single Ohio ED. After the clinical assessment of a patient, the researchers queried the providers about 3 patient-specific issues: (1) the likelihood of querying the state's prescription drug monitoring program, called Ohio Automated Rx Reporting System; (2) the likelihood of providing an opioid prescription at discharge; and (3) if yes, which opioid and what quantity. They were then provided with a printout of the patient data from the prescription drug monitoring program and asked to reassess the same questions. Of the 179 patients with complete data, information from the Ohio Automated Rx Reporting System altered prescribing practice in 74 of 179 (41%). The majority (61%) of these patients received fewer or no opioids, whereas 39% received more. The change in management was attributed to the number of previous prescriptions, 30 of 74 (41%); number of previous prescribers, 23 of 74 (31%); number of pharmacies used, 19 of 74 (26%); and number of addresses listed, 12 of 74 (16%). A limitation of this study was that 4 prescribers accounted for almost two thirds of the total patient encounters. In this study, knowledge of the information provided by a prescription drug monitoring program had an important impact on the prescription practices for controlled substances in an ED, although the actual effect of prescription drug monitoring program data on patient outcomes in this study is unknown.

Although not specifically evaluating the benefit of prescription drug monitoring programs on identifying high-risk patients, Hall et al,[32] in a Class III study, reviewed characteristics of decedents who died of prescription drugs in West Virginia and reported that opioid analgesics accounted for 93% of deaths. Cross-referencing the medical examiner's detailed analysis of the cause of death with the West Virginia prescription monitoring program, the authors determined the prescription history of the drug associated with each fatality. Patients who had received controlled drugs from 5 or more prescribers in the year before death were defined as engaging in "doctor shopping," whereas those whose death was not associated with a valid prescription were considered to have obtained their drugs through "diversion." Of the 295 deaths that were reviewed, the mean age of patients who died was 39 years, and 92% were between ages 18 and 54 years. Diversion was associated with 186 (63%) of the fatalities, and doctor shopping was associated with 63 (21%) of the fatalities. Of the 295 total decedents, 279 (95%) had at least 1 indicator of substance abuse, and these differed according to whether the drug was obtained through diversion or doctor shopping. Deaths involving diversion were associated with a history of substance abuse (82.3% versus 71.6%; odds ratio [OR] 1.8; 95% confidence interval [CI] 1.0 to 3.4), nonmedical route of pharmaceutical administration (26.3% versus 15.6%; OR 1.9; 95% CI 1.0 to 3.8), and a contributory illicit drug (19.4% versus 10.1%; OR 2.1; 95% CI 1.0 to 4.9). Patients with evidence of doctor shopping were significantly more likely to have had a previous overdose (30.2% versus 13.4%; OR 2.8; 95% CI 1.4 to 5.6) and significantly less likely to have used contributory alcohol (7.9% versus 19.8%; OR 0.3; 95% CI 0.1 to 0.9). Few patients (8.1%) were involved in both doctor shopping and diversion. The study suggests that the information provided by a prescription drug monitoring program, with correct interpretation and action based on that knowledge, might have prevented some inappropriate prescribing and poor outcomes in this patient population.

In another Class III study, Pradel et al[33] monitored prescribing trends for buprenorphine in a select area of France, using a prescription drug database during a multiple-year period. During this time, a prescription drug monitoring program was implemented, allowing a before-after comparison of the buprenorphine prescribing pattern for more than 2,600 patients. The doctor shopping drug quantity, which was defined as the total drug quantity received by the patient minus the quantity prescribed by an individual provider, increased from 631 g in the first 6 months of 2000 to a peak of 1,151 g in the first 6 months of 2004, equivalent to 143,750 days of treatment at 8 mg/day. The doctor shopping ratio, determined as the ratio of the quantity delivered to the quantity prescribed, increased steadily from early 2000 (14.9% of the grams of drug prescribed) to a peak value in the first 6 months of 2004 (21.7%). After implementation of the prescription drug monitoring program in early 2004, this value decreased rapidly, in fewer than 2 years reaching the value observed in 2000. The points of inflection of the doctor shopping curves (quantity and ratio) coincided with the implementation of the prescription drug monitoring program, suggesting an immediate benefit of this program. The prescribed quantity did not change after the implementation, indicating that access to treatment may not have changed. Eighty percent of the total doctor shopping quantity of buprenorphine was obtained by approximately 200 (8%) of the total patients. However, it is difficult to make any inferences about the effect of a decrease in doctor shopping, given the fractional amount of total prescribing accounted for by this practice.[33] The authors suggested that the doubling in the street price of buprenorphine after the prescription drug monitoring program implementation was an indicator of success.

An observational study of opioid-related deaths by Paulozzi et al[37] highlights some important considerations in the assessment of the effectiveness of prescription drug monitoring programs. The authors assessed the mortality rate from 1999 to 2005 from schedule II and III prescription opioids in the United States and compared states that had prescription drug monitoring programs with those that did not. They further divided states with prescription drug monitoring programs into those that proactively informed prescribers, generally by mail, of potential

misuse and those that did not. This study found no difference in the mortality rates over time for states with and without a prescription drug monitoring program, nor did states with proactive prescription drug monitoring programs perform better than those with programs that were not proactive. There was a nonsignificantly lower rate of consumption of schedule II opioids and a significantly higher rate of consumption of hydrocodone (schedule III) in states that had a prescription drug monitoring program. A major limitation of this study is that the variability in the prescription drug monitoring program structure, including the ability of health care providers to access the database, was not considered. Current applicability is somewhat limited by substantial changes in the manner in which prescription drug monitoring programs function since the study was conducted, including the extent of physician access and the definition of patient inclusion criteria. Because of the practical limitation of the delay in informing the prescriber of a patient's potential drug misuse, the proactive notification aspect of these programs would have minimal effect on emergency medical practice in states that cannot provide prescription drug monitoring program data in real time.

In conclusion, there are no studies that directly evaluate the effect of real-time, voluntary access to a prescription drug monitoring program on prescribing practices of emergency physicians. In addition, the broader effect of such access on diversion, abuse, doctor shopping, mortality, and the possibility of pain undertreatment remains undefined. Prescription drug monitoring programs have many limitations in their current format, including complex access issues, limitations on access permission, thresholds for patient listing, timeliness, interstate communication, and whether the data are presented to the physician automatically or require physician effort to retrieve. Furthermore, the recent addition of prescription drug monitoring programs in several states and continuing changes in the structure or function of existing programs limit the direct application of even recently published research. Legislation designed to improve prescription drug monitoring program operation (eg, NASPER) has stalled or remained underfunded, and concerns over patient confidentiality have often trumped public health concerns. Until an interstate, frequently updated, multiple-drug-schedule, easily accessible, widely used prescription drug monitoring system is implemented, the likelihood of success is limited.[35]

2. In the adult ED patient with acute low back pain, are prescriptions for opioids more effective during the acute phase than other medications?

Recommendations

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations. (1) For the patient being discharged from the ED with acute low back pain, the emergency physician should ascertain whether nonopioid analgesics and nonpharmacologic therapies will be adequate for initial pain management.

(2) Given a lack of demonstrated evidence of superior efficacy of either opioid or nonopioid analgesics and the individual and community risks associated with opioid use, misuse, and abuse, opioids should be reserved for more severe pain or pain refractory to other analgesics rather than routinely prescribed.

(3) If opioids are indicated, the prescription should be for the lowest practical dose for a limited duration (eg, <1 week), and the prescriber should consider the patient's risk for opioid misuse, abuse, or diversion.

Key words/phrases for literature searches: acute low back pain, opioid, and variations and combinations of the key words/phrases.

Acute low back pain is a common ED presenting complaint. Opioids are frequently prescribed, expected, or requested for such presentations.[40,41] In a recent study, it was estimated that low back pain–related disorders result in approximately 2.6 million annual ED visits in the United States. Of medications either administered in the ED or prescribed at discharge, the most frequently used classes were opioids (61.7%; 95% CI 59.2% to 64.2%), nonsteroidal anti-inflammatory drugs (NSAIDs) (49.6%; 95% CI 46.7% to 52.3%), and muscle relaxants (42.8%; 95% CI 40.2% to 45.4%).[41] The opioid analgesics most commonly prescribed for low back pain, hydrocodone and oxycodone products, are also those most prevalent in a Government Accountability Office study of frequently abused drugs.[42] Low back pain as a presenting complaint was also observed in a recent study to be associated with patients at higher risk for opioid abuse.[43] Low back pain, although a common acute presentation, is also often persistent and recurrent, with 33% of patients continuing to complain of moderate-intensity pain and 15% of severe pain at 1 year from initial presentation. Symptoms recur in 50% to 80% of people within the first year.[44] In one study, 19% reported opioid use at a 3-month follow-up.[40] Emergency physicians, as a specialty, are among the higher prescribers of opioid pain relievers for patients aged 10 to 40 years.[20] Recent data show simultaneous increases in overall opioid sales rates and prescription opioid–related deaths and addiction rates and suggest that widespread use of opioids has adverse consequences for patients and communities.[8]

There is a paucity of literature that addresses the use of opioids after ED discharge for acute low back pain versus the use of NSAIDs or the combination of NSAIDs and muscle relaxants. Two meta-analyses published in the last 5 years identified relatively few valid studies that address the use of opioids for low back pain.[45,46]

In a Class III 2008 Cochrane review, NSAIDs were compared with opioids and muscle relaxants for the treatment of low back pain.[46] Three studies were reviewed that compared opioids (2 of which are no longer in use) with NSAIDs for treatment of acute low back pain, including 1 study considered by the Cochrane reviewers to be of higher quality.[47] None of

the individual studies found statistically significant differences in pain relief. A Class III review by McIntosh and Hall[45] of clinical evidence for treatment of acute low back pain similarly found no evidence for superiority of opioids over other therapies and no direct information to demonstrate that opioids were better than no active therapy; however, the authors concluded that the opioid-related studies were too small to detect any clinically important differences.

A Class III Cochrane review of NSAID treatment for acute low back pain evaluated 65 studies (including more than 11,000 patients) of mixed methodological quality that compared various NSAIDs with placebo, other drugs, other therapies, and other NSAIDs.[46] The review authors concluded that NSAIDs are slightly effective for short-term symptomatic relief in patients with acute and chronic low back pain without sciatica (pain and tingling radiating down the leg). In patients with acute sciatica, no difference in effect between NSAIDs and placebo was found but moderate efficacy was found for opioids. The systematic review also reported that NSAIDs are no more effective than other drugs (acetaminophen, opioids, and muscle relaxants). Placebo and acetaminophen had fewer adverse effects than NSAIDs, and NSAIDS had fewer adverse effects than muscle relaxants or opioids.

A 2003 Cochrane review of muscle relaxants for low back pain (Class X because it did not address the role of opioids) found that muscle relaxants were effective for short-term symptomatic relief in patients with acute and chronic low back pain.[48] However, muscle relaxants were associated with a high incidence of adverse effects. This study cited strong evidence in 4 trials involving a total of 294 people that oral nonbenzodiazepine muscle relaxants are more effective than placebo in patients with acute low back pain for short-term pain relief, global efficacy, and improvement of physical outcomes.

Although no superiority has been demonstrated for opioids over other therapies for treatment of acute low back pain, groups have recommended against use of opioids as first-line therapy for treatment of this problem.[49,50] A guideline for diagnosis and treatment of low back pain endorsed by the American College of Physicians and the American Pain Society recommends opioids only for severe, disabling pain that is not controlled or not likely to be controlled with acetaminophen or NSAIDs.[49] In their 2007 guidelines, the American College of Occupational and Environmental Medicine stated that routine use of opioids for acute, subacute, or chronic low back pain is not recommended.[50]

Several observational non-ED studies also suggest caution with regard to opioid prescribing for back pain. Franklin et al,[51] in a retrospective study (Class X because of the non-ED patient population), found that workers with acute low back injury and worker's compensation claims who were treated with prescription opioids within 6 weeks of acute injury for more than 7 days had a significantly higher risk for long-term disability. In a subsequent Class III population-based prospective study of opioid use among injured Washington State workers with low back pain, Franklin et al[52] observed a strong association between the amount of prescribed opioids received early after injury and long-term use of prescription opioids. A retrospective study of 98 workers with acute low back pain and subsequent disability claims by Mahmud et al[53] found that patients whose treatment of new work-related low back pain involved opioid use for 7 days or more were more likely to have long-term disability (relative risk 2.58; 95% CI 1.22 to 5.47); however, the direct applicability of this study (Class X) was limited because most patients were not seen in the ED. In another study that addressed associations of long-term outcome with opioid therapy for nonspecific low back pain, Volinn et al[54] found that the odds of chronic work loss were 11 to 14 times greater for claimants treated with schedule II ("strong") opioids compared with those not treated with opioids at all. They further observed that the strong associations between schedule II use and long-term disability suggest that for most workers, opioid therapy did not arrest the cycle of work loss and pain. Although this study was also graded as Class X because of the population selected and failure to directly address acute or immediate benefit, the results highlight potential problems of treating acute low back pain with opioids.[54] Unfortunately, causation cannot be directly inferred from these studies because of possible confounding.

In summary, although opioids currently offer the most potent form of pain relief, there is essentially no published evidence that the prescription of opioid analgesics for acute low back pain provides benefit over other available medications or vice versa. Several observational studies suggest associations of both prescription of "strong" opioids or longer prescription duration (greater than 7 days) and early opioid prescribing with worsened functional outcomes. Additionally, as noted, the overall increased rate of opioid sales has been strongly associated with adverse effects in the community (overdose, addiction, aberrant use, and death).[8] Therefore, it can be recommended that opioids not be routinely prescribed for acute low back pain but reserved for select ED patients with more severe pain (eg, sciatica) or pain refractory to other drug and treatment modalities. Prescriptions for opioids should always be provided for limited amounts and for a limited period. Extra caution (such as use of prescription drug monitoring programs and seeking of collateral patient information such as patient visit history) may be indicated for patients identified as possibly having an increased risk for substance dependence or abuse.

3. In the adult ED patient for whom opioid prescription is considered appropriate for treatment of new-onset acute pain, are short-acting schedule II opioids more effective than short-acting schedule III opioids?

Recommendations

Level A recommendations. None specified.

Level B recommendations. For the short-term relief of acute musculoskeletal pain, emergency physicians may prescribe short-acting opioids such as oxycodone or hydrocodone

products while considering the benefits and risks for the individual patient.

Level C recommendations. Research evidence to support superior pain relief for short-acting schedule II over schedule III opioids is inadequate.

Key words/phrases for literature searches: opioids, schedule II narcotics, schedule III narcotics, acute pain, acute disease, emergency service, and variations and combinations of the key words/phrases.

Schedules II and III are classifications established by the Comprehensive Drug Abuse Prevention and Control Act of 1970 and determined by the Drug Enforcement Administration. Among other criteria, classification decisions for specific drugs are based on judgments about the potential for their abuse. Schedule II opioids include morphine (eg, MS Contin), oxymorphone (eg, Opana), oxycodone (eg, Roxicodone) and oxycodone combination products (eg, Percocet, Percodan), as well as hydromorphone (eg, Dilaudid) and fentanyl (eg, Duragesic patch, Actiq). Schedule III opioids include combination products, such as hydrocodone (15 mg or less) combined with acetaminophen (eg, Vicodin, Lortab) or ibuprofen (eg, Vicoprofen), as well as some of the codeine combination products.[55] Schedule classifications for opioids may change over time in response to a number of factors, including their perceived risk of abuse. Calls to reclassify hydrocodone combination products (eg, Vicodin, Lortab) from schedule III to schedule II have increased in recent years in response to increasing levels of abuse of these substances.

These recommendations address only new-onset acute pain. Long-acting or extended-released schedule II products such as oxycodone ER (OxyContin), methadone, fentanyl patches, or morphine extended-release (MS Contin) are indicated for chronic pain and should not be used for acute pain.[56] Long-acting and extended-release opioids are for use in opioid-tolerant patients only and are not intended for use as an "as-needed" analgesic. In addition, the immediate-release oral transmucosal formulations of fentanyl are indicated only for breakthrough pain relief in cancer patients who are already taking sustained-release medications and are opioid tolerant. These formulations should not be used for acute new-onset pain.

As part of the decision to prescribe opioids for new onset of acute pain, the care provider can select between short-acting schedule II or III agents (Table). In general, equianalgesic doses of opioids are equally efficacious in relieving pain. Therefore, *a priori*, there is no reason to consider an equianalgesic dose of a short-acting schedule II opioid more effective in providing pain relief than a short-acting schedule III opioid. However, some studies have compared schedule II and III opioids combined with nonopioid analgesics with one another. Two prospective randomized controlled trials have compared the efficacy of short-acting oxycodone, a schedule II drug, with hydrocodone combination products (schedule III) and found them to be equal.[57,58] In 2005, Marco et al[57] compared single doses of oxycodone 5 mg with hydrocodone 5 mg (both combined with 325 mg acetaminophen). In this single-site Class II study of 67 adolescent and adult subjects with acute fractures, no differences in analgesic efficacy were observed at 30 or 60 minutes. Constipation rates were higher for hydrocodone. In a 2002 Class I study, Palangio et al[58] compared oxycodone 5 mg combined with acetaminophen 325 mg (schedule II) with hydrocodone 7.5 mg combined with ibuprofen 200 mg (schedule III) in a prospective, multicenter, multidose, randomized controlled trial of 147 adults with acute or recurrent low back pain. During an 8-day study period, no differences were found in pain relief, doses taken, global evaluations of efficacy, health status, or pain interference with work. As noted above, equianalgesic doses of opioids have similar efficacy in the treatment of acute pain, no matter their Drug Enforcement Administration classification. Given this understanding, it was not unexpected that 2 randomized controlled trials comparing schedule II with III agents found no differences in analgesic efficacy.

Table. Short-acting oral opioid formulations. Dose and interval are recommended starting dosing ranges.

Medication	Initial Dose/Interval	Schedule
Codeine/APAP	30-60 mg* PO Q4-6h PRN	III
Codeine	30-60 mg PO Q4-6h PRN	II
Hydrocodone/APAP	5-15 mg* PO Q4-6h PRN	III
Hydromorphone	2-4 mg PO Q4-6h PRN	II
Morphine	15-30 mg PO Q4-6h PRN	II
Oxycodone/APAP	5-15 mg* PO Q4-6h PRN	II
Oxycodone	5-15 mg PO Q4-6h PRN	II
Oxymorphone	10-20 mg PO Q4-6h PRN	II

APAP, acetaminophen; *h*, hour; *mg*, milligram; *PO*, by mouth; *PRN*, as needed; *Q*, every.
*Listed dose is of the opioid component. Note that the acetaminophen component is now limited to 325 mg or less per pill.

4. In the adult ED patient with an acute exacerbation of noncancer chronic pain, do the benefits of prescribing opioids on discharge from the ED outweigh the potential harms?

Recommendations

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations. (1) Physicians should avoid the routine prescribing of outpatient opioids for a patient with an acute exacerbation of chronic noncancer pain seen in the ED.

(2) If opioids are prescribed on discharge, the prescription should be for the lowest practical dose for a limited duration (eg, <1 week), and the prescriber should consider the patient's risk for opioid misuse, abuse, or diversion.

(3) The clinician should, if practicable, honor existing patient-physician pain contracts/treatment agreements and

consider past prescription patterns from information sources such as prescription drug monitoring programs.

Key words/phrases for literature searches: opioid, patient discharge, pain, emergency service, and variations and combinations of the key words/phrases with exclusion of cancer.

Patients with chronic noncancer pain, either already taking opioids or not, commonly present to the ED for treatment of acute exacerbation of their pain. There have been no studies that evaluate the efficacy or potential harms of prescribing opioids specifically for these patients on discharge from the ED. Thus, given the paucity of evidence, this critical question cannot be definitively answered. Despite the biological plausibility that treating any acute exacerbation of pain with parenteral or oral opioids should decrease pain intensity, no studies were found to support this hypothesis.

Only 2 randomized controlled trials were identified that addressed the use of short-acting opioids for the treatment of breakthrough pain in patients taking opioids for chronic noncancer pain; transmucosal fentanyl was the intervention for both trials.[59,60] Because of methodological problems, valid estimates for efficacy of the intervention could not be determined, but adverse event rates among both treated populations were common and similar (range 63% to 65%) (Class III).

A systematic review of nonrandomized studies by Devulder et al[61] examined the effect of rescue medications on overall analgesic efficacy and adverse events. They examined 48 studies of patients treated with long-acting opioids for chronic noncancer pain and compared the analgesic efficacy and adverse events among those that allowed short-acting opioid rescue medications for breakthrough pain with those that did not allow such rescue medications. Although graded Class X because of lack of randomized studies and the limitation of harms studied to adverse effects only, no significant difference in the analgesic efficacy between the rescue and nonrescue studies was found. There was also no difference between these 2 groups in the incidence of nausea, constipation, or somnolence. Kalso et al,[62] in a Class III systematic review, found that 80% of patients receiving opioids for chronic noncancer pain had at least 1 adverse event, including nausea (32%), constipation (41%), and somnolence (29%).

Studies of the use of opioids for chronic pain indicate that adverse effects of these drugs are common. Several studies assessed the adverse effects with the use of tramadol with acetaminophen in the treatment of patients with chronic low back pain.[63-65] All of the studies had high dropout rates and reported adverse event rates of nausea, dizziness, and somnolence between 8% and 17%. Allan et al,[66] in a nonblinded Class III study comparing transdermal fentanyl versus oral morphine, found a constipation rate of 48% in the morphine-treated patients compared with a rate of 31% in the fentanyl-treated patients. Constipation was also the major adverse effect in a Class III study by Hale et al[67] comparing oxymorphone extended release, oxycodone controlled release, and placebo. Furlan et al,[68] in a Class II meta-analysis of 41 randomized studies of opioid use in the treatment of chronic noncancer pain, found that constipation and nausea were the only significant adverse effects. Holmes et al,[69] however, in a Class III study, assessed an opioid screening instrument, the Pain Medication Questionnaire, in chronic noncancer pain patients and found that those patients with a higher score were more likely to have a substance abuse problem or request early refills of their opioid prescription. In a retrospective Class III cohort study, Jensen et al[70] conducted a 10-year follow-up on patients discharged from a pain clinic and found that chronic opioid treatment may put patients at risk for chronic depression. Unfortunately, near-universal shortcomings of these studies include the exclusion of patients with a history of substance abuse, other significant medical problems, or psychiatric disease, and lack of follow-up to detect long-term effects such as aberrant drug-related behaviors, addiction, or overdose. Therefore, studies such as these can be confounded, making the ability to draw conclusions about causality difficult.

Questions of opioid effectiveness involve the assessment of reduction in pain and improvement in function for the patient, potential patient adverse effects, and the potential harm to the community (eg, opioid diversion and abuse) from the drugs prescribed. Hall et al,[32] in a Class III retrospective analysis of 295 unintentional prescription overdose deaths, found that 93% were due to opioids, 63% represented pharmaceutical drug diversion, 21% of the patients had engaged in doctor shopping, and 95% of the patients had a history of substance abuse. Although no studies have addressed the effects related to dose and duration of prescribed opioids in this specific patient population, 2 general studies have shown a correlation between high daily opioid dose and overdose death.[71,72]

Patient assessment tools such as the Screener and Opioid Assessment for Patients with Pain (SOAPP), Opioid Risk Tool (ORT), Diagnosis, Intractability, Risk, and Efficacy (DIRE), and others to assess the risk of prescription opioid misuse and abuse have yet to be fully validated in the ED in terms of sensitivity, specificity, and utility.[73] Many, however, believe that use of these tools, as imperfect as they are, represents a beginning in the ability to better quantify potential risks related to opioid prescribing for outpatients.

Many patients undergoing treatment for chronic noncancer pain have pain contracts/treatment agreements with their primary care providers. These should be honored if possible in treating any acute exacerbation of their pain.[74,75] As discussed in critical question 1, use of prescription drug monitoring programs may also assist the emergency physician in making appropriate clinical decisions about the use of outpatient opioid prescriptions for these patients.

FUTURE RESEARCH

Provider pain management practices related to opioids are highly variable. In part, this variability reflects the lack of evidence to guide many of these therapeutic decisions.[76]

Although there is high-quality research assessing the treatment of acute pain with opioid analgesics during the ED encounter, there is a paucity of studies assessing the benefits of prescribing opioids for discharged ED patients with acute pain and chronic noncancer pain, especially in comparison to other analgesic drugs and pain treatment modalities. Therefore, clinical decisions and practice recommendations must rely on practice experience and consensus rather than research evidence.

ED populations typically include patients with unmet substance abuse treatment needs and psychiatric comorbidities, and many of these patients present with acute pain.[77] In almost all pain studies, these patients are excluded, leaving clinicians with little evidence-based guidance for their pain management. There are also significant research gaps in clearly understanding the long-term harms of opioids, including drug abuse and addiction, aberrant drug-related behaviors, and diversion. As mentioned above, further research and validation is needed on ED patient abuse and addiction-related assessment tools. Additional studies to characterize individual patient-related risks for opioid abuse are also greatly needed.

Although there has been recent widespread adoption of prescription monitoring programs, there remains a dearth of evidence about the effectiveness of these programs in altering physician prescribing patterns or diminishing the adverse effects of opioids in the community. For research in this area to advance, further refinement of prescribing metrics (quantity, duration, and frequency) and public health measures is required. Comparison of the functionality and effectiveness of the various state prescription drug monitoring program models may provide additional insight into developing best practices that could be adopted nationally, including the sharing of data between states. Important distinctions among the states, such as immediate online prescriber access to the prescription monitoring program, should be examined for their relative contributions. However, this type of analysis must consider baseline variability among states for prescription opioid misuse (versus heroin or methadone, for example) and other state-specific issues (such as prescription-writing regulations).

With respect to the treatment of acute low back pain in the ED, there is a need for quality studies comparing the effectiveness of the more commonly prescribed opioids (hydrocodone and oxycodone congeners and other semisynthetic opioids) and nonopioid therapies, with attention to confounding variables such as depression or other psychopathology. Further study is needed to validate or refute the reported associations of early or potent opioid prescribing with increased rates of disability.[51] Given the frequency of acute low back pain as an ED presentation and its association with perceived drug-seeking behavior,[78] and with apparent higher risk for misuse,[43] more attention needs to be paid to discriminatory historical or physical factors that may be predictive of drug-seeking or abuse to allow better matching of treatment modality for individual patients.

Future studies should include additional multiple-dose analgesic protocols to better understand the postdischarge experience of patients with acute pain and what would constitute optimum patient follow-up provisions. Investigators should include clinically relevant study periods (days to weeks), which vary by diagnosis; thus, trials should be stratified by specific presenting complaints, pain site, discharge diagnosis, and classification of pain type, ie, nociceptive, neuropathic, and visceral pain. In addition to measuring pain and adverse effects, functional outcomes, such as return to work or pain-related quality-of-life measures, should be included.[79] Straightforward observational studies are needed to determine the relative duration of different acute pain presentations, thus informing decisions to prescribe an appropriate number of opioid doses per prescription. Current prescribing practice often involves a "one size fits all" pattern that is encouraged by electronic prescribing software. Prescribing practices that ignore variable durations of acute pain syndromes will predictably result in undertreatment for some patients and overtreatment for others. The latter increases the likelihood that unused opioids will be diverted into nonmedical use in communities at risk.

Additional research should include evaluation of the appropriateness of patient satisfaction as a quality metric as related to patient expectations of opioids and the prevalence of providers reporting pressure through low patient satisfaction scores or administrative complaints to provide opioids when the providers believe these drugs are not medically indicated. This issue may gain increased importance with the institution of the Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) survey, which may tie some reimbursement to patient satisfaction scores. Additional work is needed to investigate what constitutes an appropriate educational curriculum in both medical school and residency for physician education concerning safe, appropriate, and judicious use of opioids.

Research addressing the treatment of chronic noncancer pain would be enhanced by the use of accepted case definitions, standardized definitions of adverse events, and validated pain measurements. Case definitions should use a similar definition of chronic, nociceptive (musculoskeletal or visceral) versus neuropathic pain, or pain by disease type (headache, low back pain, etc). Research reporting also requires more refined descriptions of opioid potency and routes of administration.

Although opioids represent a treatment modality that has long been used in patient care, it is clear by the paucity of definitive answers to the questions posed in this document and the significant number of future research issues that much work remains to be done to clarify the best use of opioids in the care of patients.

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American Chronic Pain Association and has previously been a consultant to the pharmaceutical industry.

Relevant industry relationships are those relationships with companies associated with products or services that significantly impact the specific aspect of disease addressed in the critical questions.

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Evidentiary Table.

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Hall et al[32]	2008	Retrospective, population based, observational study	Comparison of West Virginia medical examiner data with patient data from the state prescription monitoring program and opioid abuse treatment program records	Behaviors of those who died of a pharmaceutical overdose; diversion; doctor shopping; substance abuse history; type of drug	295 deaths; 67% male; 92% aged 18-54 y; 63% pharmaceutical diversion; 21% doctor shopping; 95% substance abuse history; 93% opioids	Actual source of opioids involved in death not known; single state; not validated definitions; retrospective	III
Pradel et al[33]	2009	Database	Review of prescription drug database (not prescription monitoring program) to identify amount of buprenorphine delivered, prescribed, and obtained by doctor shopping; extension of 2004 study, used multiple time period comparisons; evaluation of trends in doctor shopping over time	Determined prescribed quantity of buprenorphine, delivered quantity, and the doctor shopping quantity	Although there was some variation over time, the trend for prescribing stayed constant overall and doctor shopping decreased after 2004, associated with the change in the mechanism by which prescriptions are monitored	Reasons for multiple providers or overlapping or interrupted prescriptions unclear; did not examine risk factors for abuse	III
Baehren et al[39]	2010	Prospective, uncontrolled	Physicians prescribing analgesics for nonacute pain were asked details about the patient's prescription and then again after being informed of the prescription monitoring program search result for that patient	Change in prescription for the specific patient	179 enrolled; management changed in 41%; 61% received fewer opioids, 39% received more	Convenience sample; majority of data from 4 prescribers	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
McIntosh and Hall[45]	2011	Review of randomized controlled trials, systematic reviews, and observational studies found searching MEDLINE 1966-12/2009, EMBASE 1980 to 12/2009, and Cochrane database up to 12/2009; 49 studies met inclusion criteria	Multiple treatment modalities for acute low back pain, including oral drugs, local injections, and nondrug treatment	Clinical improvement of low back pain	NSAIDs shown to effectively improve symptoms compared with placebo, but use associated with gastrointestinal adverse effects; muscle relaxants may reduce pain and improve clinical assessment but are associated with adverse effects including drowsiness, dizziness, nausea	The studies examining the effects of analgesics such as acetaminophen or opioids were generally too small to detect any clinically important differences	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Roelofs et al[46]	2008	Cochrane review: search of MEDLINE, EMBASE, and Cochrane central registry of controlled trials up to 7/2007; 65 trials qualified for review	NSAIDs and COX-2 inhibitors administered to treat low back pain	Clinical improvement of low back pain	Review authors found NSAIDs are not more effective than other drugs (acetaminophen, opioids, and muscle relaxants); placebo and acetaminophen had fewer adverse effects than NSAIDs, although the latter had fewer adverse effects than muscle relaxants and opioids; the new COX-2 NSAIDs do not seem to be more effective than traditional NSAIDs but are associated with fewer adverse effects, particularly stomach ulcers, although other literature has shown that some COX-2 NSAIDs are associated with increased cardiovascular risk	7 studies reported on acute low back pain, 5 of which, including 1 higher-quality study, did not find any statistical differences between NSAIDs and opioids or muscle relaxants; there is moderate evidence that NSAIDs are not more effective than other drugs for acute low back pain	III
Videman et al[47]	1984	Double-blind parallel study	70 patients; comparative trial of meptazinol vs diflunisal for up to 3 wk	Patients examined at 1-wk intervals for task capability, range of motion, and subjective pain self-assessment	Both regimens produced marked improvement in most parameters, similar adverse effect profiles	No mention of patient randomization	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Franklin et al[52]	2009	Prospective cohort; Washington State workers with back injury; n=1,883	Prospective cohort of workers with back injuries interviewed at 18 days (medial) and 1 y after injury; pharmacy data obtained from computerized records; analyzed for demographic and covariates	Injury severity, pain, function, and quantities of opioids used	For long-term users total number of medications increased significantly (P=.01) from the first to the fourth quarter; after adjustment for baseline pain, function, and injury severity, the strongest predictor of longer-term opioid prescriptions was total number of medications in the first quarter; receipt of $\geq$10 mg/day medicine in first quarter more than tripled the odds of receiving opioids long term, and receipt of $\geq$40 mg/day medicine in first quarter had 6-fold odds of receiving long-term opioids; amount of prescribed opioid received early after injury predicts long-term use	Addressed progression to long-term use according to initial treatment and continuation of same	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Marco et al[57]	2005	Single site; prospective; double blind; randomized controlled trial; concealment method described; ED patients with fractures	Single dose of oxycodone 5 mg/acetaminophen 325 mg schedule II vs hydrocodone 5 mg/acetaminophen 325 mg schedule III	Primary outcomes were numeric pain scores (0-10) at 30 and 60 min	88 subjects evaluated, 73 enrolled, 67 completed ED study period, 35 to oxycodone, 32 to hydrocodone; no baseline differences, no differences in outcomes at 30 min: -0.6 (95% CI -1.8 to 0.5); 60 min -0.5 (95% CI -2.0 to 1.0); adverse effects higher for constipation with hydrocodone (21% vs 0%; (95% CI 3% to 39%)	Small sample size powered to address acute pain during the first 30 to 60 min in the ED; study also assessed adverse effects during a longer period of time; excluded history of alcohol or opioid or other substance abuse; limited time period	II
Palangio et al[58]	2002	Prospective multicenter (18 sites), randomized controlled trial, sequential assignment by computer-generated randomization schedule	Hydrocodone 7.5 mg/ibuprofen 200 mg (schedule III) vs oxycodone 5 mg/acetaminophen 325 mg (schedule II)	Primary outcome was mean daily pain relief score at endpoint (day 8 or day of discontinuation), study period up to 8 days, intention-to-treat analysis	147 subjects enrolled (75 hydrocodone/ibuprofen, 72 oxycodone/acetaminophen), adults with acute or recurrent low back pain requiring opioids, 85% completed study in both groups, mean days to endpoint 6.5 vs 6.9 days, no baseline differences, no differences in pain relief, number of pills, global evaluations, SF-36, pain interference with work, adverse events	Excluded drug or alcohol abuse, concealment methods described	I

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Portenoy et al[59]	2007	Randomized, double blind, placebo controlled	Fentanyl buccal tablet for breakthrough pain in chronic low back pain patients	Pain before treatment and for 2 h after treatment	Fentanyl buccal tablet effective for breakthrough pain in chronic low back pain; adverse effects in 65%; 34% during double-blind phase	Severe selection bias in initial screening; industry sponsored	III for adverse effects
Simpson et al[60]	2007	Randomized, double blind, placebo controlled	Fentanyl buccal tablet for breakthrough pain in chronic pain patients	Pain before treatment and for 2 h after treatment	Fentanyl buccal tablet effective for breakthrough pain; adverse effects in 63%; 22% dropout	Severe selection bias in initial screening; industry sponsored	III for adverse effects
Kalso et al[62]	2004	Systematic review	Randomized trials in chronic noncancer pain comparing potent opioids with placebo	Pain intensity outcomes	15 randomized trials were included; 11 studies compared oral opioids for 4 wk; pain intensity decrease was 30% compared with placebo; only 44% were taking opioids by mo 7 to 24; 80% of patients experienced at least 1 adverse event: constipation (41%), nausea (32%), somnolence (29%)	4-wk duration on average; differing causes of pain; open label in many of the studies; limited power calculations; concealment not maintained in some studies	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Peloso et al[63]	2004	Prospective, randomized, blinded study	Tramadol/acetaminophen vs placebo; patients with chronic low back pain requiring daily medication for at least 3 mo	Pain VAS; pain relief rating scale; Short Form Magill Pain Questionnaire SF-36; 3-mo trial	336 patients randomized; improved mean final pain scores (47 vs 63; $P<.001$), adverse effects: nausea 12%, dizziness 11%, constipation 10%, somnolence 9%	35%-40% dropout rate; pharmaceutical-sponsored research	II
Ruoff et al[64]	2003	Prospective, randomized, blinded study	Tramadol/acetaminophen vs placebo; patients with chronic low back pain requiring daily medication for at least 3 mo	Pain VAS; pain relief rating scale; Short Form Magill Pain Questionnaire SF-36; Roland Disability Questionnaire	318 patients randomized; tramadol improved pain VAS ($P=.15$) and final Pain Relief Rating Scale ($P<.001$); adverse effects: nausea 13%, somnolence 12%, constipation 11%, dizziness 8%	153 of 318 dropped out; pharmaceutical-sponsored research	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Schnitzer et al[65]	2000	Prospective, randomized, blinded study	Tramadol/acetaminophen vs placebo; patients with chronic low back pain requiring daily medication for at least 3 mo	Time to discontinuation because of inadequate pain relief; Short Form Magill Pain Questionnaire; Roland Disability Questionnaire	380 patients in open-label phase; 254 entered into blinded phase; time to therapeutic failure was greater in the placebo group ($P<.0001$); other parameters showed improvement; adverse effects: nausea 17%, dizziness 15%, somnolence 14%, headache 12%	The dropout rate was the primary outcome; pharmaceutical-sponsored research	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Allan et al[66]	2005	Nonblinded, randomized comparison of 2 treatments in patients with chronic low back pain	Transdermal fentanyl vs sustained-release oral morphine; 680 total patients; dose titrated to effect; followed for 13 mo; outpatient setting; not applicable to ED	Pain relief (VAS scale); bowel function (validated questionnaire); quality of life (SF-36); disease, progression (3-point scale), days not working, adverse events all during 13 mo	Comparable pain relief, noninferior, VAS score for fentanyl (56) vs morphine (55); fentanyl had lower constipation rate: fentanyl (31%) vs morphine (48%)	Both groups had half of the participants drop out; vague definition of chronic low back pain; not blinded	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Hale et al[67]	2005	Randomized trial, blinded	Comparison of oxymorphone extended-release vs oxycodone controlled release vs placebo in patients with chronic low back pain who were taking a stable dose of opioids	VAS of pain score 4 h after morning dose; use of breakthrough pain medications; categorical pain intensity, pain intensity, global assessment, adverse events	Opioids were superior to placebo at reducing VAS for pain compared with placebo, oxymorphone (-27), oxycodone (-36); oxymorphone was comparable to oxycodone in pain efficacy and adverse effects; sedation and constipation were more common with opioids (35% vs 29% vs 11%)	Only 22 of 75 patients in the placebo group completed the study; included only patients receiving stable opioids and then randomized to opioids or placebo; baseline characteristics between groups not specified; pharmaceutical-sponsored research	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/ Comments	Class
Furlan et al[68]	2006	Meta-analysis	Study included randomized trials of any opioid for chronic noncancer pain (defined as pain for longer than 6 mo) vs placebo or some other nonopioid treatment	41 randomized studies with 6,019 patients evaluated for effectiveness and adverse effects; most (80%) had nociceptive pain	81% of the studies were believed to be of high quality; dropout rates were 33% in the opioid group and 38% in the placebo group; opioids improved pain and functional outcomes compared with placebo in nociceptive and neuropathic pain; strong opioids were superior to naproxen and nortriptyline for pain relief; weak opioids were not superior; constipation and nausea were the only significant adverse effects observed	Average duration of the study was 5 wk (range 1-16 wk); adequate random patient assignment in only 17 of 41 trials; 90% of trials were pharmaceutical-sponsored research	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Holmes et al[69]	2006	Prospective cohort	Convenience sample of patients who were new at a pain clinic; Pain Medication Questionnaire was administered; patients were treated with interdisciplinary treatment and/or medications alone, depending on the results of an initial evaluation	Beck Depression Inventory; Confidential Pain questionnaire; SF-36; Million VAS; Oswestry Disability Questionnaire; Physician Risk Assessment; VAS	271 patients, divided into low-, medium-, and high-score pain medication questionnaire; high-score group was more likely to have a known substance use problem (OR 2.6), request early refills (OR 3.2), or drop out of treatment (OR 2.3)	Only 26% of patients completed the full treatment program; heterogeneous types of pain diagnosis; differing treatment plans	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Jensen et al[70]	2006	Retrospective review of cohort	Patients who were treated and discharged from a pain clinic 10 y ago; medical records were abstracted and questionnaires were sent to willing participants	Demographics, health care utilization, SF-36; Hospital Anxiety and Depression Scale; Coping Strategy Questionnaire; CAGE* test	160 patients; 60% of patients were still taking long-acting opioids; dose escalation was unusual; chronic users had lower health-related quality of life and higher occurrence of depression	160 of 279 possible patients participated; no control group	III

COX-2, cyclooxygenase-2; *ED*, emergency department; *h*, hour; *mg*, milligram; *min*, minute; *mo*, month; *NSAID*, nonsteroidal anti-inflammatory drug; *OR*, odds ratio; *SF-36*, Short-Form Health Survey; *VAS*, visual analog scale; *vs*, versus; *wk*, week; *y*, year.

*CAGE (Cutting down, Annoyed, Guilty, Eye-opener) test is a method of screening for alcoholism.

Appendix A. Literature classification schema.*

Design/Class	Therapy†	Diagnosis‡	Prognosis§
1	Randomized, controlled trial or meta-analysis of randomized trials	Prospective cohort using a criterion standard or meta-analysis of prospective studies	Population prospective cohort or meta-analysis of prospective studies
2	Nonrandomized trial	Retrospective observational	Retrospective cohort Case control
3	Case series Case report Other (eg, consensus, review)	Case series Case report Other (eg, consensus, review)	Case series Case report Other (eg, consensus, review)

*Some designs (eg, surveys) will not fit this schema and should be assessed individually.
†Objective is to measure therapeutic efficacy comparing interventions.
‡Objective is to determine the sensitivity and specificity of diagnostic tests.
§Objective is to predict outcome, including mortality and morbidity.

Appendix B. Approach to downgrading strength of evidence.

	Design/Class		
Downgrading	**1**	**2**	**3**
None	I	II	III
1 level	II	III	X
2 levels	III	X	X
Fatally flawed	X	X	X