Clinical Policy: Critical Issues Related to Opioids in Adult Patients Presenting to the Emergency Department
Clinical Policy Endorsed by the American Society of Addiction Medicine (July 27, 2020)

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ABSTRACT

This clinical policy from the American College of Emergency Physicians addresses key issues in opioid management in adult patients presenting to the emergency department. A writing subcommittee conducted a systematic review of the literature to derive evidence-based recommendations to answer the following clinical questions: (1) In adult patients experiencing opioid withdrawal, is emergency department-administered buprenorphine as effective for the management of opioid withdrawal compared with alternative management strategies? (2) In adult patients experiencing an acute painful condition, do the benefits of prescribing a short course of opioids on discharge from the emergency department outweigh the potential harms? (3) In adult patients with an acute exacerbation of noncancer chronic pain, do the benefits of prescribing a short course of opioids on discharge from the emergency department outweigh the potential harms? (4) In adult patients with an acute episode of pain being discharged from the emergency department, do the harms of a short concomitant course of opioids and muscle relaxants/sedative-hypnotics outweigh the benefits? Evidence was graded and recommendations were made based on the strength of the available data.

INTRODUCTION

Opioids are synthetic or naturally occurring substances that bind to opioid receptors in humans. Activity at the μ-opioid receptor is responsible for desired effects of both euphoria and analgesia, along with negative effects such as respiratory depression. Depending on the specific opioid administered and degree of tolerance in the patient, exposure to even small amounts of potent opioids (eg, fentanyl) is often sufficient to cause respiratory depression and death. Additional adverse effects include sedation, nausea, constipation, falls, and rapid tolerance with physical dependence.

During the past decade, drug-related deaths have surpassed motor vehicle crashes as the leading cause of injury-related death in adults in the United States.[1] The percentage of deaths related to opioids increased 292% between 2001 and 2016.[2] Within some demographic groups, opioids represent a prominent cause of death; for individuals aged 24 to 35 years, opioids caused 20% of deaths.[2] In this age group, drug-induced death was the leading cause of death, exceeding that caused by motor vehicle crashes, firearms, cardiovascular disease, and neoplasm.[3] The rate of increase was initially correlated with availability of prescription opioids. In subsequent years, presumably as the medical community has become more aware of the consequences of opioid availability, the rate of increase in opioid prescription-related deaths has slowed or even declined.[4] Unfortunately, opioid-related deaths have not ceased because cheap and widely available heroin appears to have replaced prescription opioids for many individuals with opioid use disorders (OUDs).[5,6] Fentanyl and its derivatives added to or substituting for heroin are a causal factor in driving the death rate even higher.[7]

Between 2001 and 2010, emergency department (ED) visits in which opioids were administered or prescribed increased from 20.8% to 31.0%.[8] This correlated with a broader shift toward opioid-based pain management in the larger community of medicine and was not an issue unique to emergency medicine. However, trends in ED opioid prescribing appear to have stabilized and may have peaked.[9] In 2012, a cross-sectional study of discharged patients in 19 EDs revealed that 17% of ED visits resulted in an opioid prescription during the week studied.[10] This represents an ED contribution of 4.4% of all opioids prescribed in the US health care system in that year, down from 7.4% in 1996.[11] Despite serving as a minor source of opioids within the health care system, liberal ED opioid prescribing has been linked to problem use, dependence, and opioid-related death.[12,13] Consequently, the true relationship between ED opioid prescribing and the opioid epidemic remains unclear.

Nevertheless, the burden of managing this problem is increasingly falling on emergency physicians, with a rising rate of substance-use-related ED visits in the United States.[14] Emergency physicians are on the front lines, regularly treating opioid overdoses and other adverse effects such as injection-drug-related complications, OUD, and opioid withdrawal. Presently, the pent-up demand for treatment of OUD overwhelms the supply of treatment professionals and programs available. With 24-hour ED availability, acute withdrawal is a common primary or secondary complaint in the ED. However, treatment of opioid withdrawal has not been emphasized in emergency physician training until recently, so many may feel unprepared to adequately treat this now common presentation.

Comprehensive opioid-prescribing guidelines supported by systematic reviews of the literature are rarely specifically targeted toward emergency physicians, with a much greater emphasis on long-term opioid use for chronic pain and quantification of opioid use in daily morphine milligram equivalents (MMEs). This metric may be clinically useful in chronic prescribing but does not translate well to concrete recommendations for ED prescribing for acute complaints; thus, policy

recommendations developed outside of emergency medicine have rarely been applicable to the ED setting. In the past decade, various cities and states have implemented policies designed to affect ED opioid prescribing. Portions of these policies relevant to the ED setting consistently focused on limiting the duration of therapy for acute complaints. Examples include Washington State (less than 14 days), New York City (3 days or less), and Ohio (3 days or less).[15-17] Vermont and Massachusetts subsequently produced regulations limiting opioid prescription duration to 7 days or less for acute complaints.[18,19] One review found 17 states with regulations concerning opioid prescribing in any setting.[20] In 2016, the Centers for Disease Control and Prevention (CDC) released national guidelines that included the following recommendation for duration of treatment of acute pain: "Three days or less will often be sufficient; more than 7 days will rarely be needed."[21] Given the national reach of the CDC guidelines, the relevance to the clinical setting, and the use of 7-day limits on duration of opioid prescribing in multiple state regulations, 7 days or less was used as a consistent definition of "short course" of prescribing within this policy.

There are no easy solutions to the opioid problem. Balancing patient comfort and preferences with the personal and societal costs associated with opioid use is a complex issue. The lack of firm regulation means that the individual emergency physician is tasked with considering individual risks and benefits of opioid prescribing.

This policy is an update of the 2012 American College of Emergency Physicians (ACEP) Clinical Policy on opioid prescribing.[22] Three of the previous critical questions from the 2012 policy were not updated in this version because of shifting focus of the guideline. These previous questions were related to utility of state prescription drug monitoring programs, opioid prescribing related to acute low back pain, and short-acting schedule II versus schedule III opioids. For this policy, the focus is on appropriate treatment regimens for acute opioid withdrawal, benefits and harms of short courses of short-acting opioids prescribed from the ED for acute and chronic pain, and co-prescribing of opioids along with other sedating medications. Opioid use for specific conditions is addressed within ACEP complaint-specific policies, the most recent example being the discussion of opioid use for acute headache discussed in the 2019 ACEP Clinical Policy on headaches.[23] In addition, this policy does not discuss naloxone prescribing from the ED, although ACEP has issued a policy statement recommending naloxone prescribing to at-risk patients being discharged.[24]

METHODOLOGY

This Clinical Policy is based on a systematic review with critical analysis of the medical literature meeting the inclusion criteria. Searches of MEDLINE, MEDLINE InProcess, SCOPUS, EMBASE, Web of Science, and the Cochrane Database of Systematic Reviews were performed. All searches were limited to studies of adult humans and were published in English. Specific key words/phrases, years used in the searches, dates of searches, and study selection are identified under each critical question. In addition, relevant articles from the bibliographies of included studies and more recent articles identified by committee members and reviewers were included.

This policy is a product of the ACEP Clinical Policy development process, including internal and external review, and is based on the existing literature; when literature was not available, consensus of Clinical Policies Committee members was used and noted as such in the recommendation (ie, Consensus recommendation). Internal and external review comments were received from emergency physicians, clinical pharmacists, the American Academy of Clinical Toxicology, the American Board of Emergency Medicine, the American Society of Addiction Medicine, ACEP's Medical-Legal Committee, and ACEP's Quality and Patient Safety Committee. Comments were received during a 60-day open-comment period, with notices of the comment period sent in an e-mail to ACEP members, published in *EM Today*, and posted on the ACEP Web site, and sent to other pertinent physician organizations. The responses were used to further refine and enhance this Clinical Policy; however, responses do not imply endorsement. Clinical Policies are scheduled for revision every 3 years; however, interim reviews are conducted when technology, methodology, or the practice environment changes significantly. ACEP was the funding source for this Clinical Policy.

Assessment of Classes of Evidence

Two methodologists independently graded and assigned a preliminary Class of Evidence for all articles used in the formulation of this Clinical Policy. Class of Evidence is delineated whereby an article with design 1 represents the strongest study design and subsequent design classes (ie, design 2 and design 3) represent respectively weaker study designs for therapeutic, diagnostic, or prognostic studies, or meta-analyses (Appendix A). Articles are then graded on dimensions related to the study's methodological features, such as randomization processes, blinding, allocation concealment, methods of data collection, outcome

measures and their assessment, selection and misclassification biases, sample size, generalizability, data management, analyses, congruence of results and conclusions, and conflicts of interest. Using a predetermined process combining the study's design, methodological quality, and applicability to the critical question, articles received a Class of Evidence grade. An adjudication process involving discussion with the original methodologist graders and at least one additional methodologist was then used to address any discordance in original grading, resulting in a final Class of Evidence assignment (ie, Class I, Class II, Class III, or Class X) (Appendix B). Articles identified with fatal flaws or ultimately determined to not be applicable to the critical question received a Class of Evidence grade "X" and were not used in formulating recommendations for this policy. However, content in these articles may have been used to formulate the background and to inform expert consensus in the absence of robust evidence. Grading was done with respect to the specific critical questions; thus, the Class of Evidence for any one study may vary according to the question for which it is being considered. As such, it was possible for a single article to receive a different Class of Evidence rating when addressing a different critical question. Question-specific Classes of Evidence grading may be found in the Evidentiary Table included at the end of this policy.

Translation of Classes of Evidence to Recommendation Levels

Based on the strength of evidence grading for each critical question (ie, Evidentiary Table), the subcommittee drafted the recommendations and the supporting text synthesizing the evidence, using the following guidelines:

Level A recommendations. Generally accepted principles for patient care that reflect a high degree of scientific clinical certainty (eg, based on evidence from 1 or more Class of Evidence I or multiple Class of Evidence II studies demonstrating consistent effects or estimates).

Level B recommendations. Recommendations for patient care that may identify a particular strategy or range of strategies that reflect moderate scientific certainty (eg, based on evidence from 1 or more Class of Evidence II studies or multiple Class of Evidence III studies demonstrating consistent effects or estimates).

Level C recommendations. Recommendations for patient care that are based on evidence from Class of Evidence III studies or, in the absence of any adequate published literature, based on expert consensus. In

instances where consensus recommendations are made, "consensus" is placed in parentheses at the end of the recommendation.

The recommendations and evidence synthesis were then reviewed and revised by the Clinical Policies Committee, which was informed by additional evidence or context gained from reviewers.

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 consistency of results, uncertainty about effect magnitude, and publication bias, among others, might lead to a downgrading of recommendations.

When possible, clinically oriented statistics (eg, likelihood ratios [LRs], number needed to treat) are presented to help the reader better understand how the results may be applied to the individual patient. This can assist the clinician in applying the recommendations to most patients but allows adjustment when applying to patients at the extremes of risk (Appendix C).

This policy is not intended to be a complete manual on opioid management in the adult ED patient but rather a focused examination of critical issues that have particular relevance to the current practice of emergency medicine. Potential benefits and harms of implementing recommendations are briefly summarized within each critical question.

It is the goal of the Clinical Policies Committee 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 adequate empirical data to answer a critical question, the members of the Clinical Policies Committee believe that it is equally important to alert emergency physicians to this fact.

This clinical policy is not intended to represent a legal standard of care for emergency physicians. Recommendations offered in this policy are not intended to represent the only diagnostic or management options available to the emergency physician. ACEP recognizes the importance of the individual physician's judgment and patient preferences. This guideline provides clinical strategies for which medical literature exists to answer the critical questions addressed in this policy.

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

Inclusion Criteria. This guideline is intended for adult patients presenting in unscheduled acute care settings.

Exclusion Criteria. This guideline is not intended for use with pediatric patients.

CRITICAL QUESTIONS

1. **In adult patients experiencing opioid withdrawal, is ED-administered buprenorphine as effective for the management of opioid withdrawal compared with alternative management strategies?**

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. When possible, treat opioid withdrawal in the ED with buprenorphine or methadone as a more effective option compared with nonopioid-based management strategies such as the combination of α_2-adrenergic agonists and antiemetics.

Level C recommendations. Preferentially treat opioid withdrawal in the ED with buprenorphine rather than methadone.

Potential Benefits of Implementing the Recommendations:

- Adequate treatment of significant opioid withdrawal with the potential for engaging in medication for addiction treatment (also referred to as medications for OUD, or, historically, medical/medication-assisted treatment) for OUD.

Potential Harms of Implementing the Recommendations:

- Potential precipitation of opioid withdrawal after receiving buprenorphine in the patient who is opioid dependent but not yet showing signs/symptoms of opioid withdrawal, although this complication can be overcome with sufficient buprenorphine dosing.
- Adverse effects of buprenorphine, including the potential for respiratory depression, although respiratory depression is rare unless the patient is also receiving sedatives/hypnotics such as benzodiazepines.
- Given the duration of action of methadone, there is a possible increased risk of opioid toxicity in a patient given methadone in the ED who is discharged and subsequently uses additional opioids. This risk is not present with buprenorphine therapy because of its affinity for the μ-receptor and partial agonist activity, resulting in a ceiling on respiratory depression.

Key words/phrases for literature searches: benzodiazepine, buprenorphine, buprenorphine naloxone, clonidine, heroin, heroin dependence, heroin dependency, heroin withdrawal, lofexidine, methadone, methadone naloxone, methadone treatment, morphine dependence, morphine dependency, morphine withdrawal, opiate addiction, opioid analgesics, opioid-related disorder, opioid withdrawal, tapentadol, tramadol, analgesics, antiemetics, fluid therapy, oral rehydration, rehydration solutions, rehydration therapy, substance withdrawal, substance withdrawal syndrome, withdrawal syndrome, ambulatory care, outpatient care, outpatient clinic, outpatient treatment, emergency department, emergency health service, emergency room, emergency services, emergency ward, outpatient care, outpatient clinic, outpatient department, outpatient treatment, and variations and combinations of the key words/phrases. Searches included January 1, 2007, to the search dates of March 9, 2017, and August 8, 2018.

Study Selection: Two hundred fifteen articles were identified in the searches. Eight articles were selected from the search results as potentially addressing this question and were candidates for further review. After grading for methodological rigor, zero Class I studies, zero Class II studies, and 3 Class III studies were included for this critical question (Appendix D).

Opioid withdrawal

The common signs and symptoms of opioid withdrawal include cravings, abdominal cramping, nausea, vomiting, diarrhea, agitation, anxiety, feelings of hopelessness, dysphoria, piloerection, and myalgias. Onset of these symptoms from the last exposure to an opioid can vary according to the half-life of the opioid and the amount consumed, nominally 12 hours for heroin and up to 30 hours for methadone. Opioid withdrawal may be very uncomfortable but is rarely directly life threatening as a sole condition. However, patients are often motivated to avoid these distressing symptoms through continued hazardous opioid use.

Treatment of opioid withdrawal may be symptomatic, often involving the use of α_2-adrenergic agonists such as clonidine or lofexidine as well as antiemetics, atypical antipsychotics, and other medications targeting the withdrawal symptoms. However, appropriate use of buprenorphine or methadone effectively alleviates withdrawal symptoms. Initial dosing may also serve to initiate medication for addiction treatment (MAT) for OUD.

Buprenorphine

Buprenorphine is a semisynthetic derivative of the opioid alkaloid thebaine that is a more potent (25 to 40 times) and longer-lasting analgesic than morphine, with a half-life of 24 hours or more. It appears to act primarily as a partial agonist at μ-opioid receptors. Buprenorphine was first synthesized in 1966 as a synthetic opioid analgesic. Prescribing for pain indications is controlled in a fashion

similar to that of other opioids given that it is currently a Schedule III drug in the United States.

Buprenorphine was approved by the Food and Drug Administration for the treatment of OUD/opioid dependence in 2002. Initially, severe restrictions were placed on the administering and prescribing of buprenorphine to treat OUD. The Drug Addiction Treatment Act of 2000 allowed the Secretary of Health and Human Services to provide a waiver (commonly termed the "X-waiver") to physicians to administer and prescribe buprenorphine for the treatment of OUD if they have completed a special 8-hour training course. However, any Drug Enforcement Administration-licensed physicians who have not achieved the waiver may still administer buprenorphine in the ED to treat patients in opioid withdrawal, with the following restrictions:

"[They may] administer (but not prescribe) narcotic drugs to patients for the purpose of relieving acute withdrawal symptoms while arranging for the patient's referral for treatment, under the following conditions:
- Not more than one day's medication may be administered or given to a patient at one time
- Treatment may not be carried out for more than 72 hours
- The 72-hour period cannot be renewed or extended."[25]

(Note: "arranging for patient's referral for treatment" is not further described or clarified; this is frequently interpreted as a minimum obligation to provide the patient with treatment referral information in written form.)

Although individual institutions have developed internal treatment plans, there is no nationwide standard protocol for treating opioid withdrawal in the ED with buprenorphine. One example of a buprenorphine-based algorithm is included below (Figure), although no specific protocol has been well studied in the ED environment.

Methadone

Methadone is a synthetic, long-acting, Schedule II opioid used to treat OUD and is also used for pain management. Outpatient prescription for OUD is strictly controlled and drugs may be dispensed only as part of an opioid treatment program. However, like buprenorphine, methadone administration to treat OUD for up to 72 hours is allowed without participation in an opioid treatment program. Before the widespread availability of buprenorphine, ED administration of a single dose of methadone was considered the most effective opioid-based therapy to treat acute withdrawal. Nevertheless, because of its long duration of action (hours to days) lasting beyond the ED visit, as well as the potential to interfere with ongoing opioid treatment program adherence, methadone administration to alleviate acute opioid withdrawal is not common in many EDs.

Nonopioid treatment for opioid withdrawal

Nonopioid treatment for opioid withdrawal may include the administration of α_2-adrenergic agonists, antiemetics, benzodiazepines, and antidiarrheals. α_2-Agonists for treatment of symptomatic patients with nonhypotensive opioid withdrawal include clonidine and lofexidine. Nausea and vomiting may be treated with promethazine or other antiemetics. Benzodiazepines may help reduce catecholamine release during withdrawal and help alleviate muscle cramps as well as anxiety. Diarrhea can be treated with loperamide.

Effectiveness of buprenorphine in the treatment of opioid withdrawal

Gowing et al,[27] in an updated Cochrane review (Class III), assessed 27 studies using buprenorphine for the treatment of withdrawal that satisfied their criteria for inclusion. The majority of these studies were on inpatient populations. They concluded, based on quality of evidence ranging from very low to moderate, that patients receiving buprenorphine for withdrawal/detoxification compared with clonidine or lofexidine (α_2-adrenergic agonist approved in the United States in 2018) had less severe signs and symptoms of withdrawal, had fewer adverse effects, and were more likely to stay in treatment longer. They also concluded that buprenorphine is probably similar in effectiveness to tapered doses of methadone in the treatment of opioid withdrawal.

Meader,[28] in a 2010 meta-analysis of 20 randomized controlled trials (Class III), determined that buprenorphine and methadone were the most effective methods of opioid detoxification, with the former potentially being most effective. This was followed by lofexidine and clonidine, respectively. The duration of treatment in these studies ranged from 3 to 30 days, which makes direct translation to the ED setting less certain.

In a Class III systematic review, Amato et al[29] compared tapered-dose methadone with multiple other treatment modalities, one of which was buprenorphine. They found that slow tapering of long-acting opioids can reduce severity of withdrawal symptoms. Seventeen of the 23 studies included in the meta-analysis were inpatient based, again with uncertain applicability to ED care.
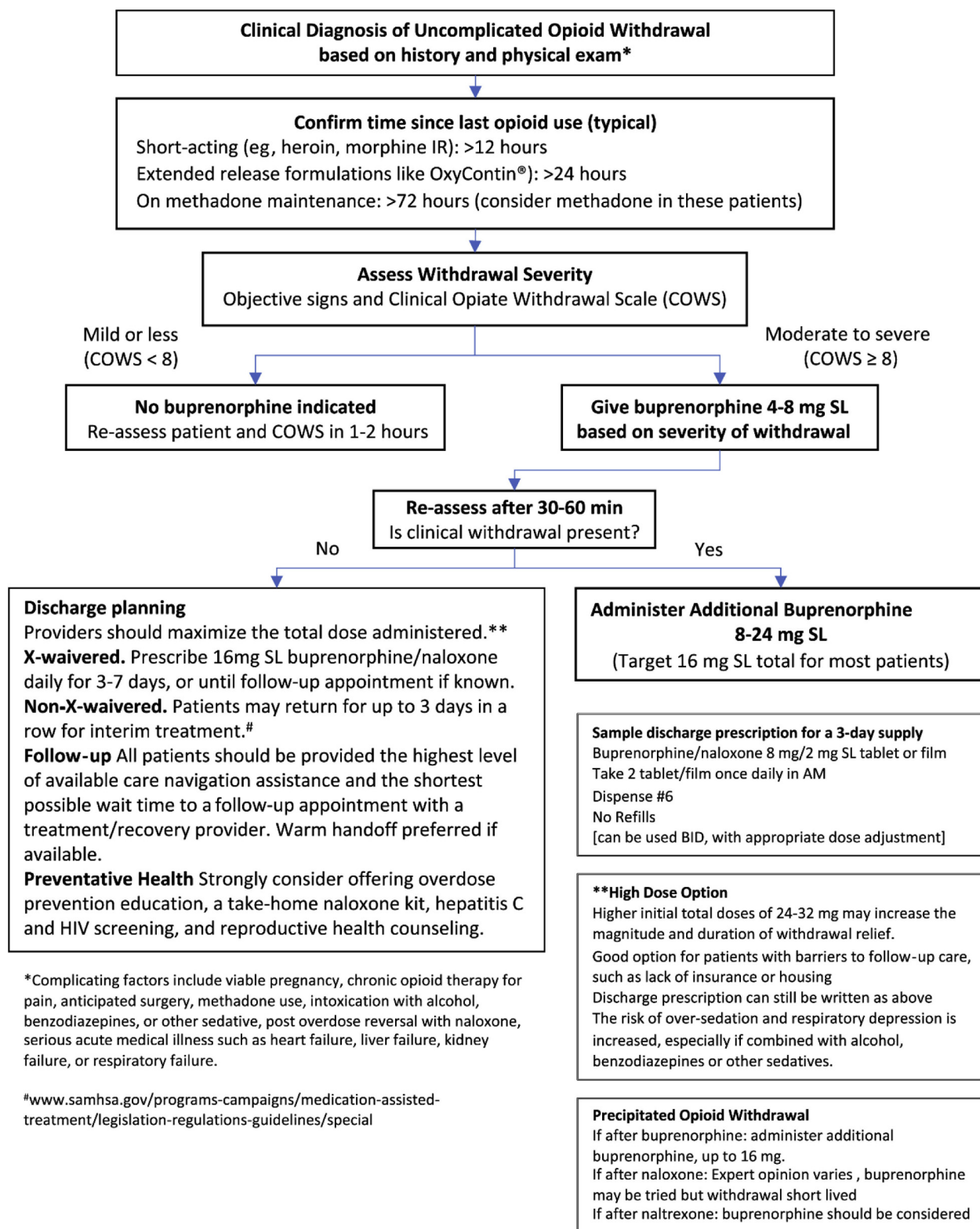
Clinical Diagnosis of Uncomplicated Opioid Withdrawal based on history and physical exam*

↓

Confirm time since last opioid use (typical)
Short-acting (eg, heroin, morphine IR): >12 hours
Extended release formulations like OxyContin®): >24 hours
On methadone maintenance: >72 hours (consider methadone in these patients)

↓

Assess Withdrawal Severity
Objective signs and Clinical Opiate Withdrawal Scale (COWS)

Mild or less
(COWS < 8)

Moderate to severe
(COWS ≥ 8)

No buprenorphine indicated
Re-assess patient and COWS in 1-2 hours

Give buprenorphine 4-8 mg SL based on severity of withdrawal

↓

Re-assess after 30-60 min
Is clinical withdrawal present?

No   Yes

Discharge planning
Providers should maximize the total dose administered.**
X-waivered. Prescribe 16mg SL buprenorphine/naloxone daily for 3-7 days, or until follow-up appointment if known.
Non-X-waivered. Patients may return for up to 3 days in a row for interim treatment.#
Follow-up All patients should be provided the highest level of available care navigation assistance and the shortest possible wait time to a follow-up appointment with a treatment/recovery provider. Warm handoff preferred if available.
Preventative Health Strongly consider offering overdose prevention education, a take-home naloxone kit, hepatitis C and HIV screening, and reproductive health counseling.

*Complicating factors include viable pregnancy, chronic opioid therapy for pain, anticipated surgery, methadone use, intoxication with alcohol, benzodiazepines, or other sedative, post overdose reversal with naloxone, serious acute medical illness such as heart failure, liver failure, kidney failure, or respiratory failure.

#www.samhsa.gov/programs-campaigns/medication-assisted-treatment/legislation-regulations-guidelines/special

Administer Additional Buprenorphine 8-24 mg SL
(Target 16 mg SL total for most patients)

Sample discharge prescription for a 3-day supply
Buprenorphine/naloxone 8 mg/2 mg SL tablet or film
Take 2 tablet/film once daily in AM
Dispense #6
No Refills
[can be used BID, with appropriate dose adjustment]

**High Dose Option
Higher initial total doses of 24-32 mg may increase the magnitude and duration of withdrawal relief.
Good option for patients with barriers to follow-up care, such as lack of insurance or housing
Discharge prescription can still be written as above
The risk of over-sedation and respiratory depression is increased, especially if combined with alcohol, benzodiazepines or other sedatives.

Precipitated Opioid Withdrawal
If after buprenorphine: administer additional buprenorphine, up to 16 mg.
If after naloxone: Expert opinion varies , buprenorphine may be tried but withdrawal short lived
If after naltrexone: buprenorphine should be considered

Figure. Algorithm for treatment of opioid withdrawal.[26] (Used with permission). *The Clinical Opiate Withdrawal Scale (COWS) can be found in Appendix E.

Medication for addiction treatment

Medication for addiction treatment is the use of Food and Drug Administration–approved medications, in combination with counseling and behavioral therapies, to provide a "whole-patient" approach to the treatment of substance use disorders. For patients with OUD, this treatment may involve the administration of methadone, buprenorphine, or extended-release naltrexone. This approach has demonstrated effectiveness and saves lives.[30] Medication for addiction treatment has been initiated in many EDs, with the typical goal of continuation of the program on an outpatient basis.[31-33] These programs have demonstrated better short-term improvement in treatment and illicit opioid use rates over referral only or brief intervention.

Cautions in using buprenorphine to treat opioid withdrawal in the ED:

- Buprenorphine should be administered only to patients in active opioid withdrawal as confirmed by history and physical examination. Because of its high binding affinity and partial agonist properties, it may induce significant withdrawal symptoms if the patient is currently receiving opioids and not yet in withdrawal. In addition, particular care is required when transitioning from methadone to buprenorphine because of risk of severe and prolonged precipitated withdrawal. Several tools (such as the Clinical Opiate Withdrawal Scale) may be used to assist in the assessment of severity of withdrawal.[34]
- Comprehensive data on buprenorphine dosing in opioid withdrawal in the ED are evolving. Monitoring best practices related to buprenorphine is prudent as these are continuing to evolve. Additional useful information on buprenorphine use in withdrawal is also available at http://www.drugabuse.gov/ed-buprenorphine and http://www.medicine.yale.edu/edbup.

Summary

Although there is a paucity of quality studies concerning the administration of buprenorphine to treat opioid withdrawal in the ED, several systematic reviews (based mainly on inpatient studies) would imply that buprenorphine administration is a safe and effective treatment for opioid withdrawal and potentially superior to other modalities of opioid withdrawal treatment.

Future Research

Future areas of research should include the following:

- Clinical trials to evaluate the effectiveness and safety of treating ED patients in opioid withdrawal with buprenorphine are needed.

- Further studies to better determine the best ED induction dose of buprenorphine before ED discharge are needed.
- Evaluation of injectable depot buprenorphine in the ED for subacute opioid withdrawal treatment after discharge is needed.
- Determination of appropriate use of buprenorphine after withdrawal has been precipitated by naloxone as well as the utility of administering buprenorphine as an alternative to naloxone in the setting of acute opioid overdose, given its affinity for opioid receptors, partial agonist activity at those receptors, and ceiling on respiratory depression.

2. **In adult patients experiencing an acute painful condition, do the benefits of prescribing a short course of opioids on discharge from the ED outweigh the potential harms?**

Patient Management Recommendations

Level A recommendations. None specified.
Level B recommendations. None specified.
Level C recommendations. Preferentially prescribe nonopioid analgesic therapies (nonpharmacologic and pharmacologic) rather than opioids as the initial treatment of acute pain in patients discharged from the ED.

For cases in which opioid medications are deemed necessary, prescribe the lowest effective dose of a short-acting opioid for the shortest time indicated.

Potential Benefits of Implementing the Recommendations:

- By limiting the number of opioid prescriptions written on discharge from the ED and limiting the duration of therapy, emergency physicians may be able to reduce the incidence of patients who develop opioid dependence and misuse, including death from opioid overdose.
- Minimizing opioids for acute conditions may prevent patients from developing unnecessary adverse effects when alternative medication or therapies with less severe adverse effects are available.
- Prescription of nonopioid therapies avoids the potential for development of opioid-induced hyperalgesia and resulting long-term challenges in providing effective pain management.

Potential Harms of Implementing the Recommendations:

- Excessive limitations on opioid prescribing for ED patients may lead to cases of inadequate pain management.

Key words/phrases for literature searches: opiate, opioid, opioids, analgesia, analgesic agent, analgesics, opioid analgesics, narcotics, drug prescriptions, drug therapy, prescription drug, acute pain, pain, pain management, back pain, bone fractures, contusion, dental pain, fractures, low back pain, neck pain, sprains, strains, toothache, addiction, adverse effect, death, drug dependence, drug dependency, overdose, readmission, treatment outcome, nephrolithiasis, emergencies, emergency, emergency department, emergency health services, emergency room, emergency services, and variations and combinations of the key words/phrases. Searches included January 1, 2007, to the search dates of March 9, 2017, and August 8, 2018.

Study Selection: Three hundred articles were identified in the searches. Twenty-two articles were selected from the search results as potentially addressing this question and were candidates for further review. After grading for methodological rigor, zero Class I studies, zero Class II studies, and 5 Class III studies were included for this critical question (Appendix D).

Emergency physicians are tasked with determining the initial course of analgesia in patients discharged after a visit for an acute painful condition. Given the individual patient and public health risks of widespread opioid prescribing, many individuals are reconsidering the duration, dose, and even the need for opioid prescriptions. The median amount of opioid actually consumed by patients after an ED visit for an acute painful condition resulting in an opioid prescription is rather limited, at less than 50 MME.[35] Such a finding suggests that most patients find limited amounts sufficient for analgesic purposes. Furthermore, higher doses and increased duration may lead to adverse consequences. The CDC has observed that there is an increased risk for opioid-naive patients to develop long-term opioid use beginning with the third day of therapy.[36] In addition, for patients susceptible to the development of OUD, it is not clear that any opioid prescription is without risk. A survey of ED patients with current opioid dependence found that greater than one third of these patients self-reported they first became exposed to opioids through legitimate prescriptions for acute painful conditions. In 11% of the ED population with current opioid dependence, the index prescription came from an ED visit.[37] This presents a challenge for emergency physicians because there is not an accurate method of predicting which patients will develop OUD or experience adverse effects from the medication and which patients, if any, will benefit from opioid therapy at discharge. This policy does not address the administration of opioids to active patients undergoing treatment in the ED; rather, it is focused on the prescription of opioids to patients being discharged after a visit for an acute painful condition.

Although it may be difficult to predict which patients discharged from the ED with opioid prescriptions will develop OUD, there is consistent evidence suggesting that opioid-naive ED patients are at increased risk for developing OUD compared with those who have used opioids previously. In a Class III study, Hoppe et al[38] found that 17% of patients discharged from EDs leave with a prescription for opioids. Most of these prescriptions were written for patients with diagnoses of back pain, abdominal pain, and extremity injuries. Nearly all of these patients received a short course (median 15 pills) of short-acting opioids. They found that opioid-naive patients who fill a prescription for opioids have an adjusted odds ratio of 1.8 (95% confidence interval [CI] 1.3 to 2.3) that they will experience recurrent use of opioids within 1 year.[38]

Another Class III study examined opioid-naive patients treated in the ED for an ankle sprain. Delgado et al[39] reported that 4.9% (95% CI 1.8% to 8.1%) of patients prescribed greater than 225 MMEs (equivalent to 30 doses of oxycodone 5 mg) transitioned to prolonged use of opioids. Prolonged use was defined as at least 4 opioid prescriptions in the next 1 to 6 months. In contrast, 1.1% (95% CI 0.7% to 1.5%) of patients prescribed less than 75 MMEs and 0.5% (95% CI 0.4% to 0.6%) of those not receiving an opioid prescription transitioned to prolonged use.

Meisel et al[40] conducted a Class III study of ED patients without an opioid prescription in the past 12 months and found that 13.7% of those filling a new opioid prescription went on to fill persistent or high-risk opioid prescriptions in the next 12 months compared with 3.2% of those not receiving opioids at the initial visit. The highest rate of conversion to persistent or high-risk use (37.3%) was observed in patients receiving a prescription for at least 350 MMEs at the initial visit, although rates were greater than 10% even for those with an initial prescription for less than 350 MMEs. These 3 studies consistently demonstrate that the development of problem opioid use in opioid-naive patients is associated with ED prescriptions of opioids, and that this relationship strengthens with increasing amounts of opioid prescribed at the initial visit.

Although the literature examining the effectiveness of opioid prescriptions compared with nonopioid therapies after ED visits is limited, 2 Class III studies examining pain management in patients presenting with acute low back pain

were identified. Innes et al[41] conducted a multicenter, randomized controlled trial of oral ketorolac versus acetaminophen/codeine. Analgesic efficacy and functional capacity did not differ between the groups. However, compared with those receiving ketorolac, more patients in the opioid group reported at least one adverse drug events (64% versus 34%), as well as serious adverse drug events (17% versus 3%). Seven of the 59 patients receiving codeine dropped out because of the severity of adverse drug events, and only 46% had a favorable view of tolerability compared with no dropouts of the 62 patients in the ketorolac group and 70% with a favorable opinion of drug tolerability. In another Class III randomized controlled study, Friedman et al[42] showed that discharged ED patients with low back pain who received oxycodone in addition to naproxen did not have improved pain benefit after 7 days compared with those receiving naproxen alone. In addition, patients receiving oxycodone were 19% more likely (95% CI 7% to 31%) to have adverse reactions such as drowsiness, dizziness, and nausea/vomiting. Thus, in addition to the long-term risks inherent to opioid therapy, there is no evidence available demonstrating that opioids provide superior pain management compared with nonopioid therapies on discharge from the ED after a visit for an acute painful condition. Furthermore, opioids are associated with increased rates of adverse events that limit tolerability.

Summary

Opioid prescribing in the ED, even when limited to short-acting, low-potency medications for a few days of therapy, is not risk free. Patients may experience immediate adverse effects such as nausea, vomiting, over-sedation, and respiratory depression. In addition, these patients are at risk for developing an OUD, complications from chronic opioid use, and death from overdose. Therefore, opioid prescribing from the ED for an acute painful condition should be reserved for patients for whom there is a need for pain relief and alternative therapies are expected to be ineffective or are contraindicated. In those cases, anticipated risks and benefits along with alternatives should be discussed with the patient. If deemed appropriate, only low-dose, short-acting opioids with a short duration of therapy should be prescribed.

Future Research

Future areas of research should include the following:
- Methods of identifying ED patients at high risk for development of an OUD if prescribed opioids as treatment for an acute painful condition.
- Comparison of effectiveness of opioid therapy versus nonopioid analgesics/nonpharmacologic therapies in

discharged ED patients treated for various acute painful conditions.
- Evaluation of educational interventions in the ED to increase patient understanding of the adverse effects of opioids and risks of dependence and opioid misuse.
- Trials evaluating efficacy and safety of more or less euphoric opioids in discharged ED patients.

3. **In adult patients with an acute exacerbation of noncancer chronic pain, do the benefits of prescribing a short course of opioids on discharge from the ED outweigh the potential harms?**

Patient Management Recommendations

Level A recommendations. None specified.
Level B recommendations. None specified.
Level C recommendations. Do not routinely prescribe opioids to treat an acute exacerbation of noncancer chronic pain for patients discharged from the ED. Nonopioid analgesic therapies (nonpharmacologic and pharmacologic) should be used preferentially.

For cases in which opioid medications are deemed appropriate, prescribe the lowest indicated dose of a short-acting opioid for the shortest time that is feasible.

Potential Benefits of Implementing the Recommendations:
- Avoid exposing patients to an increased risk of developing OUD.
- Avoid potential immediate adverse effects associated with opioid use; specifically, vomiting, but also nausea, constipation, dizziness, drowsiness, headache, pruritus, and dry mouth.

Potential Harms of Implementing the Recommendations:
- Withholding a treatment associated with a statistically significant, but small, improvement in pain control compared with placebo (but not to nonopioid alternatives).

Key words/phrases for literature searches: opiate, opioid, opioids, opioid analgesic, acute pain, chronic pain, musculoskeletal pain, cancer, musculoskeletal diseases, neoplasms, drug prescriptions, prescription drugs, drug administration schedule, medication adherence, opioid abuse, opioid overdose, opioid-related disorders, drug overdose, risk assessment, patient discharge, hospitalization, patient readmission, emergency room, emergency services, and variations and combinations of the key words/phrases. Searches included January 1, 2012, to the search dates of March 9, 2017, April 12, 2017, and August 8, 2018.

Study Selection: Nine hundred twenty-four articles were identified in the searches. Thirty-nine were selected from the search results as potentially addressing this question and were candidates for further review. After grading for methodological rigor, zero Class I studies, zero Class II studies, and 3 Class III studies were included for this critical question (Appendix D).

Patients with chronic noncancer pain frequently present to the ED for treatment of acute exacerbations of their chronic pain. Unfortunately, there have been no studies that evaluate the efficacy or potential harms of prescribing a short course of opioids on discharge from the ED among this specific patient population. Although the paucity of directly applicable studies precludes giving a more definitive answer to this question, there is existing literature that allows reasonable inferences to be made about the potential risks and benefits of prescribing a short course of opioids to patients with an acute exacerbation of their chronic noncancer pain. The scope of this question specifically excludes pain management for sickle cell disease because the committee recognizes that hospitals frequently develop multidisciplinary therapeutic protocols that guide analgesia in this population, limiting emergency physician discretion. Consequently, because of concerns that studies of sickle cell patients treated in the ED may not be generalizable to other patients presenting with chronic noncancer pain, the literature search for this recommendation excluded the sickle cell population.

Three Class III studies were identified. The first of these is a systematic review by Busse et al[43] of randomized clinical trials that examined the harms and benefits of opioids for patients with chronic noncancer pain. The review examined 96 trials including 26,169 participants treated with opioids for control of their chronic noncancer pain, and the efficacy of opioids for pain control and physical functioning compared with placebo, as well as with other nonopioid analgesic options (including nonsteroidal anti-inflammatory drugs [NSAIDs], tricyclic antidepressants, anticonvulsants, and synthetic cannabinoids). The authors also considered the adverse effects (vomiting, nausea, constipation, dizziness, drowsiness, headache, pruritis, and dry mouth) of opioids therapy compared with placebo. They found that opioids did not provide a level of analgesic benefit that reached the predetermined threshold for a minimally important reduction in pain (1 cm on a 10-cm visual analog scale) compared with placebo (weighted mean difference −0.79 cm [95% CI −0.90 to −0.68 cm] on a 10-cm visual analog scale for pain). Similarly, opioids did not result in meaningful improvement in physical functioning (5 points on a 100-point Short Form-36 physical component score),

with a weighted mean difference of 2.04 points (95% CI 1.41 to 2.68 points). These findings are supported by high-quality evidence from 42 and 51 randomized controlled trials, respectively. In terms of adverse effects, opioids were found to result in significant increases in all measured adverse effects, with vomiting having the most pronounced difference, 5.9% with opioids versus 2.3% with placebo (relative risk 2.50 [95% CI 1.89 to 3.30]; risk difference 3.6% [95% CI 2.1% to 5.4%]). In contrast to the evidence comparing opioids with placebo that is examined in this review, the evidence comparing opioids with nonopioid medications for analgesia was of overall low to moderate quality; however, opioids were not found to be superior to any of the comparator groups. More specifically, moderate-quality evidence found no difference between opioids and NSAIDs for either pain relief (weighted mean difference −0.60 cm [95% CI −1.54 to 0.34 cm] on the 10-cm visual analog scale for pain) or physical functioning (weighted mean difference −0.90 points [95% CI −2.69 to 0.89 points] on the 100-point Short Form-36 physical component score), but did find that opioids were associated with an increase in vomiting compared with NSAIDs (relative risk 4.71 [95% CI 2.92 to 7.60]; risk difference 6.3% [95% CI 3.2% to 11.1%]).

Beyond the immediate potential adverse effects of opioid use, there is significant concern that patients with chronic noncancer pain who are prescribed opioids are at risk of developing an OUD. There are 2 large non-ED–based retrospective studies that provide an estimation of the strength of association of opioid prescription with adverse outcomes. A 2014 Class III study[44] examined patients with a new episode of chronic noncancer pain who had not received opioids in the previous 6 months, and who carried no previous diagnosis of an OUD. In this study, Edlund et al[44] found that patients prescribed opioids had a significantly higher risk of developing OUDs compared with those not prescribed opioids, even among those who received what they termed low-dose (0 to 36 MMEs/day), acute (1 to 90 days) prescriptions (odds ratio 3.03; 95% CI 2.32 to 3.95). The risk was markedly increased for patients who received opioids for greater than 90 days, and the magnitude of the risk increased substantially in this long-term opioid use group, depending on dose (odds ratio 14.92, 28.69, and 122.45 for the low-, medium-, and high-dose groups, respectively). Individuals with a diagnosis of mental health disorders, alcohol use disorder, and nonopioid drug use disorders were also found to be at increased risk of developing OUD after being prescribed opioids for their chronic noncancer pain.

A 2017 Class III study by the CDC[36] examined the association between first opioid use among opioid-naive

patients without cancer and the likelihood that the patient would continue to use opioids at 1 year and 3 years, stratified by treatment duration, dosage, and number of prescriptions. Among patients receiving their first opioid prescription, 2.6% continued to use opioids for at least 1 year. The authors found that the probability of long-term opioid use increased markedly after only 5 days of prescription duration (and further increased at 1 month). In this population, approximately 70% of patients received an initial prescription of less than or equal to 7 days. These studies suggest that opioid prescriptions after ED visits for exacerbations of chronic noncancer pain carry an inherent risk of development of an OUD.

Summary

Although there are no studies directly examining the effect of a short prescription of opioids for ED patients presenting with an acute exacerbation of chronic noncancer pain, a large Class III systematic review of 96 randomized controlled trials (based mainly on outpatient studies) found that opioids offered no clinically significant reduction in pain or improvement in function compared with placebo or nonopioid treatment options, but did increase adverse events (most notably vomiting).[43] Additionally, two large retrospective studies found clear associations between opioid prescriptions and the development of subsequent long-term use and OUD, even with low-dose prescriptions of short duration (as little as ≥5 days' duration).[36,44] These data all suggest that the risks of prescribing even a short course of opioids for most ED patients with acute exacerbations of chronic noncancer pain outweigh the negligible to potentially nonexistent benefits.

Future Research

Future areas of research should include the following:

- Trials evaluating both the efficacy and potential harms of prescribing a short course of opioid medication for the treatment of acute exacerbations of chronic noncancer pain.
- Comparison of frequently prescribed opioid formulations and dosages with nonopioid alternatives, particularly NSAIDs.
- Development of tools for assessing the risk that this patient population will develop either long-term opioid use or an OUD after being prescribed a short course of opioids after ED discharge.
- Strategies for preventing opioid overdose after an ED visit for treatment of acute exacerbations of chronic noncancer pain.

4. **In adult patients with an acute episode of pain being discharged from the ED, do the harms of a short concomitant course of opioids and muscle relaxants/sedative-hypnotics outweigh the benefits?**

Patient Management Recommendations

Level A recommendations. None specified.
Level B recommendations. None specified.
Level C recommendations. Do not routinely prescribe, or knowingly cause to be co-prescribed, a simultaneous course of opioids and benzodiazepines (as well as other muscle relaxants/sedative-hypnotics) for treatment of an acute episode of pain in patients discharged from the ED (Consensus recommendation).

Potential Benefits of Implementing the Recommendations:
- Reducing the severity of toxicity when opioids are combined with other centrally acting drugs.
- Preferential use of safer therapeutic alternatives.

Potential Harms of Implementing the Recommendations:
- Limited therapeutic options for patients receiving long-term opioids or muscle relaxants/sedative-hypnotics.

Key words/phrases for literature searches: opiate, opioid, opioids, analgesics, sedatives, antianxiety agents, hypnotics, muscle relaxants, baclofen, benzodiazepine, carisoprodol, cyclobenzaprine, eszopiclone, metaxalone, methocarbamol, tapentadol, tramadol, zaleplon, zolpidem, acute pain, pain, pain management, substance-related disorders, drug overdose, mortality, death, emergency, emergency department, emergency health services, emergency room, outpatient care, ambulatory care, patient discharge, patient readmission, treatment outcome, and variations and combinations of the key words/phrases. Searches included January 1, 2007, to the search dates of March 9, 2017, and August 8, 2018.

Study Selection: Four hundred articles were identified in the searches. Twenty-five articles were selected from the search results as potentially addressing this question and were candidates for further review. After grading for methodological rigor, none of the 25 articles were classified as Class I, II, or III; therefore, zero studies were included for this critical question (Appendix D).

Benzodiazepines are relatively safe when prescribed alone. However, a trend of increased mortality associated with the increased prescribing of benzodiazepines has been identified that resembles the trend of escalating overdose

mortality associated with the opioid prescriptions during the last 2 decades.[45] This burden is thought to be due to the substantial potentiation of opioid-related respiratory depression when taken in combination with centrally acting muscle relaxants/sedative-hypnotics such as benzodiazepines.[46] Emergency physicians have observed increasing rates of overdoses and drug-related deaths related to the combination of opioids and benzodiazepines.[47] Furthermore, population-based studies examining patterns of opioids and sedative-hypnotics/muscle relaxers prescribing, most prominently benzodiazepines, have identified a substantial increased risk of death when these agents are co-prescribed. In particular, the rates of death are 3- to 10-fold higher in patients co-prescribed opioids and benzodiazepines compared with opioids alone.[48,49] The literature search and evaluation process outlined in the "Methodology" section of this clinical policy yielded no directly applicable primary research study of at least a Class III level of evidence assignment. However, our understanding of the pharmacologic mechanism of these agents as well as the background literature described earlier that has examined prescribing patterns and overdose epidemiology suggests that co-prescribing is a significant danger to the ED population.

Unfortunately, there is a dearth of evidence evaluating analgesic efficacy or patient functional improvement when prescriptions for muscle relaxants (including benzodiazepines) are combined with prescriptions for opioids for acute pain when patients are discharged from an ED. However, for many common painful conditions there is a demonstrated lack of superiority when either opioids or sedative-hypnotic/muscle relaxers are prescribed compared with safer therapeutic alternatives. For example, recent meta-analyses suggest that for the treatment of acute low back pain, combination pharmacotherapy (eg, opioid with NSAID or muscle relaxant with NSAID) does not outperform monotherapy with NSAID, and that muscle relaxant drugs do not provide clinically significant additional pain relief. Furthermore, these meta-analyses suggest that co-prescribing muscle relaxants may increase risk of patient harm.[50,51] Therefore, although there is a lack of direct evidence related to ED prescribing patterns, given the increased risks of co-prescribing and lack of demonstrated benefit, the committee was able to reach consensus to develop the recommendation against routinely combining these therapies for patients being discharged from the ED after being treated for an acute episode of pain.

As the dangers of co-prescribing were being recognized in recent years, institutions focused on quality- and safety-produced guidelines, such as a recent quality measure by the National Quality Forum, titled "Safe Use of Opioids—Concurrent Prescribing" 3316e (2018), or the Department of Veterans Affairs/Department of Defense Clinical Practice Guideline for Diagnosis and Treatment of Low Back Pain (2017), which make specific recommendations against co-prescribing muscle relaxants/sedative-hypnotics (specifically benzodiazepines) along with opioids.[52,53] Moreover, the Food and Drug Administration added a black box warning in 2016 to both opioids and benzodiazepines recommending against co-prescribing these agents.[54] Unfortunately, none of these guidelines draw on studies that met inclusion criteria for this guideline.

Given the widespread potential effect on health care system policies and reimbursement, emergency physicians should become familiar with the National Quality Forum measure as its implementation increases:

National Quality Forum 3316e specifically evaluates "[p]atients age 18 years and older prescribed two or more opioids or an opioid and benzodiazepine concurrently at discharge from a hospital-based encounter (inpatient or emergency department [ED], including observation stays)."

- S.4. Numerator Statement: Patients prescribed 2 or more opioids, or an opioid and benzodiazepine at discharge.
- S.6. Denominator Statement: Patients aged 18 years and older prescribed an opioid or a benzodiazepine at discharge from a hospital-based encounter (inpatient stay less than or equal to 120 days or ED encounters, including observation stays) during the measurement period.
- S.8. Denominator Exclusions: The following encounters are excluded from the denominator:
  - Encounters for patients with an active diagnosis of cancer during the encounter
  - Encounters for patients who receive palliative care orders during the encounter
  - Inpatient encounters with length of stay greater than 120 days

Denominator exceptions: None

Summary

Although there is a paucity of quality studies concerning the co-prescribing of a short concomitant course of opioids and muscle relaxants/sedative-hypnotics for acute pain in ED patients, the evolving epidemiologic data and non-ED studies suggest that in the ED, co-prescribing of these 2 classes of medications should be done with caution, and, when possible, avoided.

Future Research

Future areas of research should include the following:

- Prospective trials evaluating optimal treatment regimens for patients with specific acute pain indications (eg, acute low back pain) who are being discharged from an ED.
- Prospective trials studying the effect of the use of state pharmacy boards' prescription drug monitoring programs or ED information exchanges to improve patient selection, and reduce risk, with respect to opioid prescriptions in patients being discharged from an ED.

Relevant industry relationships: Dr. Ketcham has worked on a joint ACEP/American Society of Addiction Medicine project related to ED initiation of medication-assisted treatment that was grant funded by Indivior, the manufacturer of Suboxone. Mitigation of this potential conflict was achieved by allowing Dr. Ketcham to participate in and contribute his experience to the content development of the critical questions; however, he was not allowed to vote when establishing the final recommendations for question 1. He was assigned to work on question 4.

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 question.

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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 series	Case series

*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.

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

Appendix C. Likelihood ratios and number needed to treat.*

LR (+)	LR (−)	
1.0	1.0	Does not change pretest probability
1–5	0.5–1	Minimally changes pretest probability
10	0.1	May be diagnostic if the result is concordant with pretest probability
20	0.05	Usually diagnostic
100	0.01	Almost always diagnostic even in the setting of low or high pretest probability

LR, likelihood ratio.
*Number needed to treat (NNT): number of patients who need to be treated to achieve 1 additional good outcome; NNT=1/absolute risk reduction×100, where absolute risk reduction is the risk difference between 2 event rates (ie, experimental and control groups).

Appendix D. PRISMA[55] flow diagrams.

Critical Question 1 Flow Diagram

Identification

Articles identified through database searching
(n = 214)

Articles records identified through other sources
(n = 1)

Articles after duplicates removed
(n = 148)

Screening

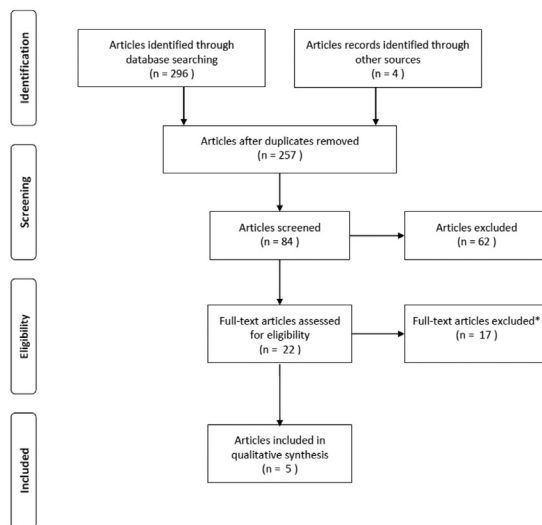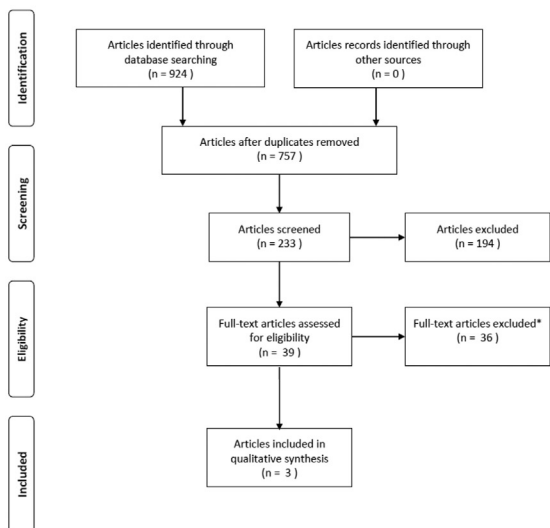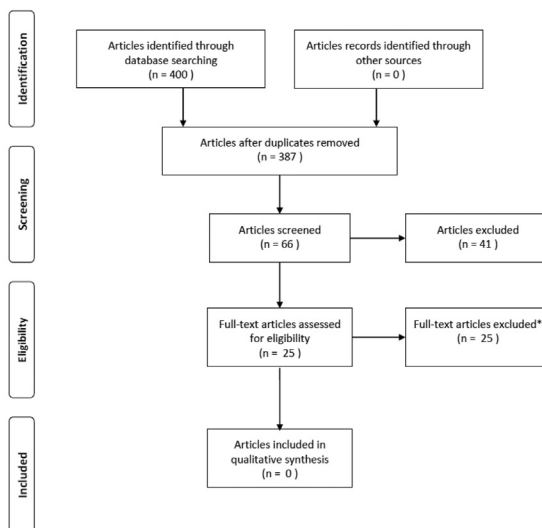Articles screened
(n = 64)

Articles excluded
(n = 56)

Eligibility

Full-text articles assessed for eligibility
(n = 8)

Full-text articles excluded*
(n = 5)

Included

Articles included in qualitative synthesis
(n = 3)

Critical Question 2 Flow Diagram

Identification

Articles identified through database searching
(n = 296)

Articles records identified through other sources
(n = 4)

Articles after duplicates removed
(n = 257)

Screening

Articles screened
(n = 84)

Articles excluded
(n = 62)

Eligibility

Full-text articles assessed for eligibility
(n = 22)

Full-text articles excluded*
(n = 17)

Included

Articles included in qualitative synthesis
(n = 5)

Critical Question 3 Flow Diagram

Identification

Articles identified through database searching
(n = 924)

Articles records identified through other sources
(n = 0)

Articles after duplicates removed
(n = 757)

Screening

Articles screened
(n = 233)

Articles excluded
(n = 194)

Eligibility

Full-text articles assessed for eligibility
(n = 39)

Full-text articles excluded*
(n = 36)

Included

Articles included in qualitative synthesis
(n = 3)

Critical Question 4 Flow Diagram

Identification

Articles identified through database searching
(n = 400)

Articles records identified through other sources
(n = 0)

Articles after duplicates removed
(n = 387)

Screening

Articles screened
(n = 66)

Articles excluded
(n = 41)

Eligibility

Full-text articles assessed for eligibility
(n = 25)

Full-text articles excluded*
(n = 25)

Included

Articles included in qualitative synthesis
(n = 0)

*Articles identified with fatal flaws or ultimately determined to not be applicable to the critical question. See "Methodology" section for more detail.

Appendix E. Clinical Opiate Withdrawal Scale (COWS)[56] (Used with permission).

Patient's Name:_____   Date and Time ____/_____/____:_____

Reason for this assessment:_____

Resting Pulse Rate: _____beats/minute *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120	**GI Upset**: *over last 1/2 hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting
Sweating: *over past 1/2 hour not accounted for by* *room temperature or patient activity.* 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	**Tremor** *observation of outstretched hands* 0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching
Restlessness *Observation during assessment* 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 unable to sit still for more than a few seconds	**Yawning** *Observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute
Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	**Anxiety or Irritability** 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable or anxious 4 patient so irritable or anxious that participation in the assessment is difficult

Bone or Joint aches *If patient was having pain*
    previously, only the additional component attributed
    to opiates withdrawal is scored
0 not present
1 mild diffuse discomfort
2 patient reports severe diffuse aching of joints/muscles
4 patient is rubbing joints or muscles and is unable to sit
    still because of discomfort
	Gooseflesh skin
	0 skin is smooth
	3 piloerrection of skin can be felt or hairs standing up
	    on arms
	5 prominent piloerrection

Runny nose or tearing *Not accounted for by cold* *symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	Total Score _____ The total score is the sum of all 11 items Initials of person completing assessment: _____

Score: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal

Evidentiary Table.

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Gowing et al[27] (2017)	III for Q1	Systematic review of RCTs of interventions of opioid withdrawal using buprenorphine; inpatient and outpatient settings; no studies in EDs	Withdrawal treatment with buprenorphine was compared with methadone, clonidine, and lofexidine; outcome measures included intensity of withdrawal, adverse effects, and rate of withdrawal treatment completion; used standard meta-analytic approaches	Included 27 studies with 3,048 participants; meta-analysis was possible for treatment duration (similar for buprenorphine and methadone) 1.3 days and treatment completion rates,risk ratio=1.04 (95% CI 0.91 to 1.2); compared with clonidine and lofexidine, buprenorphine had lower average withdrawal scores, –0.43 (95% CI –0.58to –0.28); buprenorphine patients also stayed in treatment longer and were more likely to complete treatment, risk ratio=1.6 (95% CI 1.2 to 2.1); no significant difference in adverse events; for difference in treatment completion, number needed to treat=4 (95% CI 3 to 6); for every 4 treated with buprenorphine, 1 additional person will complete treatment compared with clonidine or lofexidine; buprenorphine is more effective than clonidine or lofexidine for managing opioid withdrawal in terms of severity of withdrawal, duration of withdrawal treatment, and the likelihood of treatment completion; buprenorphine and methadone appear to be equally effective, but data are limited	No ED studies; most study participants were men, with no outcomes based on sex; 7 studies were funded or medicines provided by a pharmaceutical company; funding source unclear for 7 studies; 12 of the studies had a high risk of bias. No meta-analysis could be done for the comparison with methadone for the outcome of withdrawal or adverse effects; quality of evidence was low or moderate for comparison of buprenorphine with clonidine or lofexidine andfor comparison of buprenorphine with methadone, and very low for dose reduction

Evidentiary Table. (continued)

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Meader[28] (2010)	III for Q1	Systematic review of RCTs involving treatment with buprenorphine, methadone, clonidine, or lofexidine for opioid detoxification	Used a "mixed treatment comparison approach" in which treatments could be ranked; used WinBUGS software to do 80,000 MCMC simulations; main outcome measure appears to be only "completion of treatment"	23 RCTs identified with data on 2,112 patients; buprenorphine was more effective than clonidine (OR 3.95; 95% credible interval 2.01 to 7.46), but not for lofexidine (OR 2.64; 95% credible interval 0.9 to 7.5); buprenorphine may be more effective than methadone (OR 1.64; 95% credible interval 0.68 to 3.79); methadone was more effective than clonidine (OR 2.42; 95% credible interval 1.07 to 5.37) but not necessarily more effective than lofexidine (OR 1.62; 95% credible interval 0.6 to 4.58); buprenorphine had the highest probability (85%) of being the most effective treatment, followed by methadone (12.1%), lofexidine (2.6%), and then clonidine (0.01%); comparison between buprenorphine and methadone did not show a statistically significant difference	RCT settings not specified; criteria for "effective treatment" in the different studies not elucidated; seems to stress "completion of treatment" but with no information on other outcome measures such as withdrawal severity; unclear whether there were 2 independent reviewers of articles, unclear whether the quality of individual studies was assessed, and no mention of heterogeneity measurement/sensitivity analyses

Evidentiary Table. (continued)

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Amato et al[29] (2013)	III for Q1	Systematic review of RCTs comparing tapered methadone versus other pharmaceutical modalities for treatment of opioid withdrawal; inpatient and outpatient settings; no studies in EDs	For treatment of opioid withdrawal, tapered methadone is compared with adrenergic agonists, opioid agonists (eg, buprenorphine), anxiolytics, and placebo; outcomes: rate of treatment completion, withdrawal scores, adverse effects, relapse, abstinence at follow-up	23 trials with 2,467 patients met inclusion criteria; comparing methadone versus any other pharmacologic treatment, there was no clinical difference observed between the 2 treatments in terms of completion of treatment, 16 studies, 1,381 participants, risk ratio 1.08 (95% CI 0.97 to 1.21); number of participants abstinent at follow-up, 4 studies for tapered methadone versus buprenorphine, 390 participants, risk ratio 0.97 (95% CI 0.69 to 1.37); degree of discomfort for withdrawal symptoms and adverse events, although it was impossible to pool data for the last 2 outcomes	Although primarily directed at a review of tapered methadone for opioid withdrawal, 4 studies compared tapered methadone with buprenorphine; of these, 3 had unclear methods descriptions; 17 of the trials conducted in inpatient units; studies were not ED based
Hoppe et al[38] (2015)	III for Q2	Retrospective cohort urban academic ED in Colorado	Compared opioid-naive patients who received and filled a prescription with those who received and did not fill a prescription, and those who did not receive a prescription; defined recurrent use as having another opioid prescription filled 60 days before or 60 days after a date 5 mo after ED visit; data pulled from state prescription drug monitoring system	4,800 patients; 2,496 (52%) opioid naive; 775 (31% of opioid naive) patients filled prescription, and of these, 299 (12%) had recurrent use; for opioid-naive patients who filled a prescription vs those who did not, the OR for recurrent use was 1.8 (95% CI 1.3 to 2.3); for opioid-naive patients who received a prescription but did not fill it compared with those who did not get a prescription, the OR for recurrent use was 0.8 (95% CI 0.5 to 1.3)	Refilling a second opioid prescription does not meet definition of misuse; study limited to 1 ED setting

Evidentiary Table. (continued)

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Delgado et al[39] (2018)	III for Q2	Secondary retrospective analysis of national insurance claims from 2011 to 2015; describes the association between initial opioid prescription intensity and transition to prolonged use	Transition to prolonged use, defined by ≥4 opioid prescriptions 30 to 180 days after index visit; predictors: dosing of opioids (eg, >225 MMEs); performed logistic regression modeling	30,832 patients met inclusion criteria, 7,739 (25.1%) received opioid, median MME of 100 (IQR 75 to 113), tab quantity of 15 (IQR 12 to 20) and for a median of 3 days (IQR 2 to 4 days); among 25,849 with 6-mo continuous enrollment after index ED visit, 6,463 (25%) received an opioid prescription MMEs >225 (≥30 tabs of oxycodone 5 mg); adjusted prolonged opioid use was 4.9% (95% CI 1.8% to 8.1%) compared with 1.1% (95% CI 0.7% to 1.5%)	Reason for selecting the variables not explained in the model; appears there is no adjustment for clustering by provider or state; interaction terms and effect modification not disclosed; imputation not performed for missing data

Evidentiary Table. (continued)

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Meisel et al[40] (2019)	III for Q2	Retrospective cohort study of Washington Medicaid beneficiaries with data linked from the prescription drug monitoring program between January 1, 2013, and December 31, 2015	ED visits if the ED visit did not result in an inpatient admission and the patient was opioid naive at the visit, defined as no history of opioid dispensing during the previous 12 mo; excluded observations for enrollees with a 1-y history of cancer, those who were also enrolled in Medicare or older than 64 y, children younger than 13 y, and enrollees who received any hospice or nursing home care at any time during the study period; also excluded members who were enrolled for less than 3 of the previous 12 mo; primary outcome was a composite measure of any indicator of long-term opioid use or high-risk prescription fills within 12 mo after the index visit; logistic regression model used to assess the association between measures described above and conversion to persistent or high-risk use	Among 202,807 index ED visits, 23,381 resulted in a new opioid prescription; of these, 13.7% led to persistent or high-risk opioid prescription fills within 12 mo compared with 3.2% for patients who received no opioids at the index visit; factors associated with increased likelihood of persistent opioid or high-risk prescription fills included a history of skeletal or connective-tissue disorders; neck, back, or dental pain; and a history of prescribed benzodiazepines; the highest conversion rates (37.3%)	Study limited to opioid-naive ED visits during which a new opioid prescription was written and subsequently filled; it is possible some of the index ED visit prescriptions did not originate at that time; had access to only outpatient prescription data

Evidentiary Table. (continued)

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Innes et al[41] (1998)	III for Q2	Double-blind RCT at 6 EDs (both university and community); convenience sample of 122; after receiving either ketorolac (10 mg orally) or acetaminophen-codeine (600mg acetaminophen, 60mg codeine, respectively); subjects evaluated at 30 and 60 min and then hourly until 6 h or until second analgesic dose; to be included, had to be well enough to be discharged in 2 to 4 h; study medication received every 4 to 6 h; pain and functional capacity evaluated for up to 7 days with telephone follow-up on day 3 or 4, and final in-person assessment at 7 to 9 days; subjects instructed to record pain relief and functional capacity daily at bedtime, and overall pain relief and medication rating at study end	Outcome of visual analog score pain was performed at discharge (calculated pain intensity difference score or pain intensity difference); subjects recorded visual analog score, functional capacity, and pain relief and functional capacity daily at bedtime, and overall pain relief and medication rating at study termination; adverse effects recorded at telephone follow-up and at end; summed pain intensity difference scores computed by weighting the length of time in hours; calculated sample size n=70 subjects in each group to discern a 20% difference in treatment groups; missing data were interpolated linearly	Ketorolac patients completed diaries for 4.4 days, acetaminophen-codeine patients for 5.2 days; after day 1, 24% of ketorolac patients and 31% of acetaminophen-codeine patients reported "a lot" or "complete" relief of pain; time to peak relief was 2.6 days for both groups; 21 of 62 (34%) ketorolac patients and 38 of 59 (64%) acetaminophen-codeine patients reported at least 1 adverse drug events; neither agent was superior in terms of analgesic efficacy	Convenience sampling; target sample size not reached; no adjustment for within-subject correlations repeated-measures outcomes; and no intention-to-treat analysis

Evidentiary Table. (continued)

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Friedman et al[42] (2015)	III for Q2	3-arm double-blind RCT in high-volume urban academic ED	Patients presenting with acute low back pain; given naproxen plus placebo, muscle relaxer (cyclobenzaprine), or oxycodone; 10-day supply of medicine; outcome measures of improvement in Roland-Morris Disability Questionnaire and pain at 1 wk and 3 mo after initial ED visit	323 enrolled, 107 placebo, 108 cyclobenzaprine and oxycodone arms; at 1-wk follow-up, Roland-Morris Disability Questionnaire improvement was 9.8 in placebo, 10.1 in cyclobenzaprine, and 11.1 in oxycodone group, with no significant between-group differences; number of subsequent ED visits similar (3 placebo vs 1 cyclobenzaprine vs 3 oxycodone)	Patients received a 10-day course, not a 7-day course, of prescription; oxycodone group had a longer duration of low back pain before ED presentation (72 vs 48 hand 48 h); fewer patients in oxycodone group used the medications
Busse et al[43] (2018)	III for Q3	Systematic review of 96 RCTs; included trials (1) enrolled patients with chronic noncancer pain, (2) randomized them to an oral or transdermal opioid (pure opioid or a combination product) vs any nonopioid control, and (3) conducted follow-up for at least 4 wk	The primary outcomes were pain intensity (score range 0 to 10 cm on a visual analog scale for pain at the longest follow-up period; lower is better and the MID is 1 cm), physical functioning (score range, 0 to 100 points on the SF-36 PCS; higher is better and the MID is 5 points), and incidence of vomiting	N=26,169; compared with placebo, opioid use was associated with reduced pain (weighted mean difference −0.69 cm [95% CI −0.82 to −0.56 cm] on a 10-cm visual analog scale for pain; modeled risk difference for achieving the MID 11.9% [95% CI 9.7% to 14.1%]), improved physical functioning (weighted mean difference 2.04 points [95% CI 1.41 to 2.68 points] on the 100-point SF-36 PCS; modeled risk difference for achieving the MID 8.5% [95% CI 5.9% to 11.2%]), and increased vomiting (5.9% with opioids vs 2.3% with placebo for trials that excluded patients with adverse events during a run-inperiod)	Evidence was from studies of only low to moderate quality; assessment of long-term associations of opioids with chronic noncancer pain was not possible because no trial followed up with patients for longer than 6 mo; none of the included studies provided rates of developing opioid use disorder and only 2 reported rates of overdose; numerous outcomes and comparisons were evaluated, including subgroup analyses without adjustment for multiple comparisons; heterogeneity associated with pooled estimates for pain relief and functional improvement among trials of opioids vs placebo may have reduced evidence quality

Evidentiary Table. (continued)

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Edlund etal[44] (2014)	III for Q3	Retrospective cohort study of claims data from Health Core database from 2000 to 2005	Compared rate of developing opioid use disorder among patients with new chronic noncancer pain diagnoses who were or were not prescribed opioids	N=568,640; patients with chronic noncancer pain who were prescribed opioids had higher rate of developing opioid use disorder than those not prescribed opioids; patients prescribed opioids had significantly higher rates of opioid use disorders compared with those not prescribed opioids; effects varied by average daily dose and days' supply: low dose, acute (OR 3.03; 95% CI 2.32 to 3.95); low dose, chronic (OR 14.92; 95% CI 10.38 to 21.46); medium dose, acute (OR 2.80; 95% CI 2.12 to 3.71); medium dose, chronic (OR 28.69; 95% CI 20.02 to 41.13); high dose, acute (OR 3.10; 95% CI 1.67 to 5.77); and high dose, chronic (OR 122.45; 95% CI 72.79 to 205.99)	Included measures of painful diagnostic conditions, but no measure of pain severity or activity interference; unable to verify whether patients had an undiagnosed problem or opioid use disorder before 6 mo before opioid therapy was initiated; study included only individuals with commercial insurance

Evidentiary Table. (continued)

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Shah etal[36] (2017)	III for Q3	Retrospective convenience sample of 10% of patients in the IMS Lifelink+ database	Analyzed duration of use, number of prescriptions, and cumulative dose of patients with first-episode opioid use, time to discontinuation of opioids	N=1,294,247; 33,548 (2.6%) who continued therapy for ≥1 y; of patients who had at least 1 day of opioids, probability of continued use at 1 and 3 y was 6.0% and 2.9%, respectively	

CI, confidence interval; *cm*, centimeter; *ED*, emergency department; *h*, hour; *IQR*, interquartile range; *MID*, minimally important difference; *MME*, morphine milligram equivalent; *mo*, month; *OR*, odds ratio; *Q*, critical question; *RCT*, randomized controlled trial; *SF-36 PCS*, 36-item Short Form physical component score; *wk*, week; *y*, year.