Clinical Policy: Critical Issues Related to Opioids in Adult Patients Presenting to the Emergency Department

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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 stimulate opioid receptors in humans. Activity at the mu 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 user, the therapeutic window may be very narrow with the clinical consequence that exposure to even small amounts of potent opioids (eg, fentanyl) is sufficient to cause respiratory depression and death. Additional adverse effects include sedation, nausea, constipation, and rapid tolerance with physical dependence.

Over the past decade, drug-related deaths have surpassed motor vehicle crashes as the leading cause of injury-related death in adults in the US.[1] The percentage of deaths related to opioids increased 292% between 2001 and 2016.[2] Within some demographic groups, opioids represent a leading cause of death; for those 24 to 35 years of age, opioids caused 20% of deaths.[2] In this age group, drug induced death was the leading cause of death,

exceeding motor vehicle crashes, firearms, cardiovascular disease, and neoplasm.[3] The rate of increase was initially correlated with availability of prescription opioids. However, as the medical community has become more aware of the consequences of opioid availability, the rate of increase in prescriptions has slowed or stopped.[4] Unfortunately, deaths have not slowed, as cheap and widely available heroin appears to have replaced prescription opioids for many opioid users.[5,6] Contamination of heroin with fentanyl appears to be driving the death rate even higher.[7]

Between 2001 to 2010, emergency department (ED) visits where 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 Emergency Departments revealed that 17% of ED visits resulted in an opioid prescription during the week studied.[10] This represented 4.4% of all opioid prescriptions in the US healthcare system in that year, down from 7.4% in 1996.[11] Despite serving as a minor source of opioids within the healthcare 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 visits in the US.[14] Emergency physicians are on the front lines, regularly treating opioid overdoses and other adverse effects such as injection drug-related complications, drug dependence, and opioid withdrawal. Presently, the pent-up demand for opioid treatment overwhelms the supply of providers and programs available. With 24-hour ED availability, acute withdrawal is a common primary or secondary complaint in the ED. However, treatment of acute opioid withdrawal is rarely a primary focus of emergency physician training. Although individual institutions may have developed internal treatment plans, there is no nationwide standard protocol for treating opioid withdrawal in the ED.

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. This metric may be clinically useful in chronic prescribing but does not translate well to concrete recommendations for ED

prescribing for acute complaints, thus outside societal recommendations have rarely been applicable to the ED setting. In the past decade, various cities and states implemented policies designed to impact 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).[15,16] Vermont and Massachusetts each 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 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 provider is tasked with considering individual risks and benefits of opioid prescribing. The 2012 clinical policy attempts to meet the needs of both patients and emergency physicians in answering pressing questions related to opioids prescribed from the ED. 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.

This policy is an update of the 2012 ACEP clinical policy on opioid prescribing. Three of the previous critical questions from the 2012 policy were not updated in this version due to 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. Of note, opioid use for specific conditions is addressed within the 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.[22]

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). Clinical policies are scheduled for review 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 clinical certainty (eg, based on evidence from 1 or more Class of Evidence I or multiple Class of Evidence II studies).

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

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 emergency department 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 emergency departments (EDs).

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

Exclusion Criteria. This guideline is not intended for pediatric patients presenting in unscheduled acute care settings.

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 opioid based therapy (burprenorphine or methadone) as a more effective option compared to non-opioid based management strategies such as the combination of alpha 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 potential bridging to Medical-Assisted Treatment (MAT) for opioid use disorder.

Potential Harms of Implementing the Recommendations:

- Precipitation of significant opioid withdrawal after receiving buprenorphine in the patient who is opioid dependent but not yet showing signs/symptoms of opioid withdrawal.
- Potential side effects of buprenorphine including respiratory depression, especially if the patient is on concomitant sedatives/hypnotics such as benzodiazepines.

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: Three hundred and seventy-one articles were identified in the searches. Seven articles were selected from the search results for further review, with zero Class I studies, zero Class II studies, and 3 Class III studies included for this critical question.

Opioid withdrawal

The common symptoms of opioid withdrawal include 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 based upon 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 life threatening as a sole condition.

Treatment of opioid withdrawal often involves the use of alpha-2 adrenergic agonists such as clonidine or lofexidine as well as antiemetics and other drugs targeting the withdrawal symptoms. Judicious use of methadone or buprenorphine may alleviate withdrawal symptoms as well. These 2 drugs are often given in decreasing doses for gradual detoxification or may be given at an ongoing fixed dose to treat acute withdrawal as well as to initiate Medication Assisted Treatment (MAT) for opioid use disorder.

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 as a partial agonist at mu and kappa opioid receptors and as an antagonist at delta receptors, thus being in the group of agonist/antagonist opioids. Buprenorphine was discovered in 1966 and was approved by the Food and Drug Administration for opioid addiction treatment in 2002. It is currently a Schedule III drug in the US.

Initially, severe restrictions were placed on the administering and prescribing of buprenorphine. The Drug Addiction Treatment Act of 2000 allowed the Secretary of Health and Human Services (HHS) to provide a waiver (the so-called X-Waiver) to physicians to administer and prescribe buprenorphine for the treatment of opioid addiction and withdrawal if they have completed a special 8-hour training course. Physicians who have not achieved the waiver may still use 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."[23]

(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.)

Non-opioid treatment for opioid withdrawal

Non-opioid treatment for opioid withdrawal may include the administration of alpha-2 adrenergic agonists, antiemetics, benzodiazepines, and antidiarrheals. Common alpha-2 agonists for symptomatic non-hypotensive opioid withdrawal patients include clonidine and lofexidine. Nausea and/or 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 or octreotide. Of note, individual and combinations of non-opioid treatments appear inferior when compared to buprenorphine.

Effectiveness of buprenorphine in the treatment opioid withdrawal

Gowing et al,[24] in an updated Cochrane Review (Class III), assessed 27 studies that satisfied their criteria for inclusion. The vast majority of these studies were on inpatient populations. They concluded, based upon quality of evidence ranging from very low to moderate that patients receiving buprenorphine for withdrawal/detoxification compared to clonidine or lofexidine (alpha-2 adrenergic agonist approved in the US in 2018) had less severe signs and symptoms of withdrawal, had fewer side 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[25] in a 2010 meta-analysis of 20 randomized controlled trials (Class III) concluded 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 make application to the ED somewhat problematic.

Amato et al,[26] in a Class III systematic review, compared tapered dose methadone to multiple other treatment modalities, one of which was buprenorphine. Their conclusion was 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 little applicability to ED care.

Medication-Assisted Treatment

Medication-Assisted Treatment (MAT) is the use of FDA-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 opioid use disorder, this treatment may involve the administration of methadone, buprenorphine, or extended-release naltrexone. This approach has demonstrated effectiveness and saves lives.[27] MAT has been initiated in many EDs, with the typical goal of continuation of the program on an outpatient basis.[28] These programs have demonstrated improved short-term improvement in treatment and illicit opioid use rates over referral only or brief intervention. However, there was no observed difference in long-term (6 and 12 months) outcomes in a study of MAT initiation from the ED compared to brief intervention or referral for outpatient initiation of MAT.[29]

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

- In treating withdrawal in the ED with buprenorphine the SAMSHA guidelines mentioned above should be followed. The physician should use one of the forms of buprenorphine that have been designated as acceptable to the Drug Enforcement Administration (DEA) for treatment of opioid use disorder/opioid withdrawal (such as Suboxone, Subutex, Zubsolv, Sublocade or generic equivalents).
- Buprenorphine should only be administered to patients in active opioid withdrawal as confirmed by history and physical examination. Because of its antagonist properties, it may induce significant withdrawal symptoms if the patient is currently taking opioids and not yet in withdrawal. In addition, particular care is required when transitioning from methadone to buprenorphine, due to risk of severe and prolonged precipitated withdrawal. Several tools (such as the Clinical Opiate Withdrawal Scale [COWS]) may be used to assist in the assessment of severity of withdrawal.
- Comprehensive data on buprenorphine dosing in opioid withdrawal in the ED are lacking. One algorithm is provided by Herring, et al.[30]

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

- A clinical trial to evaluate the efficacy and effectiveness of treating ED patients in opioid withdrawal with buprenorphine.
- Further studies to better determine the best ED induction target dose of buprenorphine prior to ED discharge are needed.
- Evaluation of injectable depot buprenorphine in the ED for subacute opioid withdrawal treatment after discharge is needed.

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?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations. Preferentially prescribe nonopioid analgesic therapies (non-pharmacologic and pharmacologic) rather than opioids as the initial treatment of acute pain in patients discharged from the ED.

In cases where opioid medications are deemed appropriate, prescribe the lowest indicated dose of a short acting opioid for the shortest period of time (Consensus recommendation).

Potential Benefits of Implementing the Recommendations:

- By limiting the number of opioid prescriptions written upon 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, as well as prevent patients from developing unnecessary adverse effects from the medications when alternative medication or therapies with less severe side effects are available.

Potential Harms of Implementing the Recommendations:

- There is concern that by severely curtailing the use of opioid prescribing for ED patients there is a risk of oligoanalgesia (failure to provide analgesia in patients with acute pain).

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: Four hundred thirty-one articles were identified in the searches. Eighteen articles were selected from the search results for further review, with zero Class I studies, zero Class II studies, and 2 Class III studies were included for this critical question.

The CDC has observed that there is an increased risk for opioid naïve patients to develop long-term opioid use beginning with the third day of therapy, potentially leading to opioid use disorder.[31] A survey of ED patients with current opioid dependence found that over one third of these patient's 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.[32] The challenge for emergency providers is that it is unknown as to which patients will develop opioid dependence or misuse disorder or suffer adverse effects from the medication.

While it may be difficult to predict which patients discharged from the ED with opioid prescriptions will develop opioid use disorder, there is evidence suggesting that opioid naïve ED patients are at increased risk for developing opioid use disorder. Hoppe et al, in a Class III study, found that 17% of patients discharged from EDs leave with a prescription for opioids.[33] 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. He found that those opioid naïve patients who fill a prescription for opioids have an adjusted odds ratio of 1.8 (95% CI 1.3 to 2.3) that they will experience recurrent use of opioids within one year.[33]

Although short course ED specific literature is limited, in a randomized controlled study (Class III), Friedman et al, 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 to naproxen alone. In addition, those taking oxycodone were 19% more likely (95% CI 7% to 31%) to have adverse reactions such as drowsiness, dizziness, and nausea/vomiting.[34]

Summary

Opioid prescribing in the ED, even when done using short-acting, low-potency medications for a few days of therapy is not risk free. Patients may suffer immediate adverse effects such as nausea and vomiting and are at risk for developing dependency and even death from overdose. Therefore, opioid prescribing, even for a

short course from the ED, should be reserved for patients for whom there is a need for pain relief and alternative medications, or nonpharmacologic therapies have been ineffective or are expected to be ineffective, or are contraindicated. In those cases, risks and benefits and alternatives should be discussed with the patient and low-dose, short-acting opioids and short duration of therapy should be prescribed.

Future Research

Future areas of research should include:

- Clinical trials to evaluate interventions in the ED to increase patient understanding of the side effects of opioids and risks of dependence and opioid misuse.
- Clinical trials comparing opioid versus nonopioid analgesics and other pain treatment modalities in discharged ED patients are needed.

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?

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 (non-pharmacologic and pharmacologic) should be used preferentially.

In cases where opioid medications are deemed appropriate, prescribe the lowest indicated dose of a short acting opioid for the shortest period of time that is feasible (Consensus recommendation).

Potential Benefits of Implementing the Recommendations:

- Avoid exposing patients to an increased risk of developing opioid use disorder.
- Avoid potential immediate adverse effects associated with opioid use, specifically vomiting, but also including 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, improvements 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: One thousand one hundred ten articles were identified in the searches. Thirty-nine were selected from the search results for further review, with zero Class I studies, zero Class II studies, and 3 Class III studies were included for this critical question.

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 upon discharge from the ED among this specific patient population. While the paucity of directly applicable studies precludes giving a more definitive answer to this question, there is existing literature that allows for 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. Of note, this policy specifically excludes pain management for sickle cell disease. The recommendations contained within do not apply to the sickle cell population.

A Class III systematic review by Busse et al[35] of randomized clinical trials 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 to other nonopioid analgesic options (including nonsteroidal anti-inflammatory drugs, tricyclic antidepressants, anticonvulsants and synthetic cannabinoids). This review also examined the adverse effects (vomiting, nausea, constipation, dizziness, drowsiness, headache, pruritis, and dry mouth) of opioids compared with placebo. Overall, the authors 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, 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 side effects, with vomiting having the most pronounced difference, 5.9% with opioids versus 2.3% with placebo for trials that excluded patients with adverse events during a run-in period (relative risk 2.50 [95% CI 1.89 to 3.30], *P*<.001; risk difference 3.6% [95% CI 2.1% to 5.4%]). In contrast to the evidence comparing opioids to placebo, the evidence comparing opioids to 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, *P*=.21) 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, *P*=.33), 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], *P*<.001; risk difference 6.3% [95% CI 3.2% to 11.1%]).

Beyond the immediate potential adverse effects of opioid use, there exists the significant concern that patients with chronic noncancer pain who are prescribed opioids may be at risk of developing opioid dependence or opioid use disorder. There are 2 large non ED-based retrospective studies that provide as estimation of the strength of association of opioid prescription with adverse outcomes. A 2014 Class III study by Edlund et al[36] examined claims data for 568,640 individuals with a new episode of chronic noncancer pain, not receiving opioids in the previous 6 months and with no previous diagnosis of an opioid use disorder. They found that those prescribed opioids had significantly higher risk of developing opioid use disorders compared with those not prescribed opioids, even among those who received what they termed low dose (0 to 36 mg morphine/day), acute (1 to 90 days) prescriptions, (odds ratio 3.03; 95% CI 2.32, 3.95). The risk was markedly increased for those patients who took opioids for >90 days and the magnitude of the risk increased markedly 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 groups, respectively). Individuals diagnosed with mental health disorders, alcohol use disorder, and nonopioid drug use

disorders were also found to be at increased risk of developing opioid use disorder after being prescribed opioids for their chronic noncancer pain.

In a 2017 Class III study by the CDC,[31] examined the association between first opioid use among opioid naïve 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. The 1,294,247 patients who received their first opioid prescription between 2006 and 2015 were identified in a database as meeting the inclusion criteria, of which 33,548 (2.6%) continued to use opioids for at least 1 year. Significantly, the authors found that the probability of long-term opioid use increased most sharply in the initial days after initiating opioid use, increasing markedly after only 5 days of prescription duration (and again at 1 month). As important context, this study found that ~70% of patients received an initial prescription of less than or equal to 7 days.

Summary

Although there are no studies directly examining the impact of a short prescription of opioids for ED patients presenting with an acute exacerbation of chronic noncancer pain, a high quality systematic review of randomized control 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).[35] Two large retrospective studies found clear associations between opioid prescriptions and the development of subsequent long-term use and opioid use disorder, even with low-dose prescriptions of short duration (with clear effects evident in prescriptions of as little as ≥5 days duration).[31,36] These data would all suggest that the risks of prescribing even a short course of opioids for ED patients with acute exacerbations of chronic noncancer pain outweigh the negligible to potentially nonexistent benefits.

Future Research

Prospective trials evaluating both the efficacy and potential harms of prescribing a short course of opioid medication for the treatment of acute exacerbations of a chronic noncancer pain are needed. Studies should focus both on analgesic benefits using commonly accepted pain scale ratings and should compare frequently prescribed

opioid formulations and dosages to nonopioid alternatives, particularly NSAIDs. Studies that examine the risk of this patient population developing either long-term opioid use or opioid use disorder after being prescribed a short course of opioids after ED discharge are also essential. Ideally these studies would be able to determine the associated risk of opioid overdose among these patients as well.

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?

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:

- Reduce potential overdose risk and other potential harms dues to over-sedation.

Potential Harms of Implementing the Recommendations:

- Insufficient reduction in pain and muscle spasms.

Key words/phrases for literature searches: opiate, opioid, opioids, analgesics, sedatives, anti-anxiety 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: Five hundred thirty-four articles were identified in the searches. Twenty-five articles were selected from the search results for further review. None of the 25 articles were classified as Class I, II, or III; therefore, zero studies were included for this critical question.

Benzodiazepines are relatively safe when prescribed alone. However, similar to the trend of increased overdose mortality associated with the increased prescribing of opioids over the last 2 decades, a trend of increased mortality associated with the increased prescribing of benzodiazepines has been identified.[37] This

increased burden is thought to be due to the dramatic potentiation of opioid related respiratory depression when taken in combination.[38] These effects are evident in increasing rates of ED treatment of overdoses and drug related deaths related to the combination of opioids and benzodiazepines.[39] 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, these studies have identified an outsized risk related to co-prescribing with a 3 to 10 fold increase in death in patients co-prescribed opioids and benzodiazepines compared to opioids alone.[40,41] 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, the indirect evidence from our understanding of the pharmacologic mechanism of these agents, examination of prescribing patterns, and overdose epidemiology as described above suggest 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 combining prescriptions for muscle relaxants (including benzodiazepines) with prescriptions for opioids for acute pain when being discharged from an ED. However, there is a demonstrated lack of benefit for prescribing either opioids or sedative-hypnotic/muscle relaxers for many common painful conditions. For example, recent meta-analyses suggest that for the treatment of acute LBP, 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.[42,43] 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.

During the same period that the dangers of coprescribing were recognized, institutions focused on quality and safety have produced guidelines, such as a recent quality measure by the National Quality Forum (NQF), titled “Safe Use of Opioids – Concurrent Prescribing” #3316e (2018), or the VA/DoD Clinical Practice Guideline for Diagnosis and Treatment of Low Back Pain (2017), that make specific recommendations against co-prescribing muscle relaxants/sedative-hypnotics (and specifically benzodiazepines) along with opioids.[44,45] Moreover, the FDA added a “black box” warning in 2016 to both opioids and benzodiazepines recommending

against co-prescribing these agents.[46] Unfortunately, none of these guidelines draw upon studies that met inclusion criteria for this guideline. However, given the widespread potential impact on health care system policies and reimbursement, providers should become familiar with the NQF measure:

"NQF # 3316e" specifically evaluates "Patients 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 two or more opioids, or an opioid and benzodiazepine at discharge.
- S.6. Denominator Statement: Patients age 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 emergency department 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 are ordered for palliative care 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

- Prospective trials evaluating optimal treatment regimens for patients with specific acute pain indications (eg, acute low back pain) being discharged from an ED.
- Prospective trials studying the impact 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.

	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

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).

828 **Evidentiary Table.**

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Gowing et al[24] (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 to clonidine and lofexidine, buprenorphine had lower average withdrawal scores, -0.43 (95% CI -0.58 to -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 to 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 male with no outcomes based on gender; 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 to methadone for the outcome of withdrawal or adverse effects; quality of evidence was low or moderate for comparison of buprenorphine to clonidine or lofexidine, methadone, and very low for dose reduction

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Evidentiary Table.

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Meader[25] (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" where 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; 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 if there were 2 independent reviewers of articles, if the quality of individual studies was assessed, and no mention of heterogeneity measurement/sensitivity analyses

832 **Evidentiary Table (continued).**

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Amato et al[26] (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, side effects, relapse, abstinence at follow-up	23 trials with 2,467 patients met inclusion criteria; comparing methadone versus any other pharmacological 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 to buprenorphine – of these, 3 had unclear methods descriptions; 17 of the trials done in inpatient units; studies are not ED based
Hoppe et al[33] (2015)	III for Q2	Retrospective cohort urban academic ED in Colorado	Compared opioid naïve 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 naïve; 775 (31% of opioid naïve) patients filled prescription and of these 299 (12%) had recurrent use; for opioid naïve patients who filled a prescription vs those that did not, the OR for recurrent use was 1.8 (95% CI 1.3 to 2.3); for opioid naïve patients who received a prescription but did not fill it compared to 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 one ED setting

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834 **Evidentiary Table (continued).**

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Friedman et al[34] (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 (Flexeril), 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 versus 48 and 48 h); fewer patients in oxycodone group used the medications
Busse et al[35] (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 wks	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 versus 2.3% with placebo for trials that excluded patients with adverse events during a run-in period)	Evidence was from studies of only low to moderate quality; assessment of long-term associations of opioids with chronic non-cancer 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

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836 **Evidentiary Table (continued).**

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Edlund et al[36] (2014)	III for Q3	Retrospective cohort study of claims data from HealthCore database from 2000 to 2005	Compared rate of developing opioid use disorder among 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, 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 if patients had an undiagnosed problem or opioid use disorder prior to 6 mo before opioid therapy was initiated; study included only individuals with commercial insurance

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Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Shah et al[31] (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 over 1 y; of patients who took at least 1 day of opioids, probability of continued use at 1 y and 3 y was 6.0% and 2.9%, respectively	

CI, confidence interval; *cm*, centimeter; *ED*, emergency department; *h*, hour; *MID*, minimally important difference; *MME*, morphine milligram equivalents; *mo*, month; *NSAID*, nonsteroidal anti-inflammatory drug; *OR*, odds ratio; *RCT*, randomized controlled trial; *SF-36 PCS*, 36-item Short Form physical component score; *wk*, week; *y*, year.