Review | Annals of Internal Medicine

Opioid Prescribing: A Systematic Review and Critical Appraisal of Guidelines for Chronic Pain

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Background: Deaths due to prescription opioid overdoses have increased dramatically. High-quality guidelines could help clinicians mitigate risks associated with opioid therapy.

Purpose: To evaluate the quality and content of guidelines on the use of opioids for chronic pain.

Data Sources: MEDLINE, National Guideline Clearinghouse, specialty society Web sites, and international guideline clearinghouses (searched in July 2013).

Study Selection: Guidelines published between January 2007 and July 2013 addressing the use of opioids for chronic pain in adults were selected. Guidelines on specific settings, populations, and conditions were excluded.

Data Extraction: Guidelines and associated systematic reviews were evaluated using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument and A Measurement Tool to Assess Systematic Reviews (AMSTAR), respectively, and recommendations for mitigating opioid-related risks were compared.

Data Synthesis: Thirteen guidelines met selection criteria. Overall AGREE II scores were 3.00 to 6.20 (on a scale of 1 to 7). The AMSTAR ratings were poor to fair for 10 guidelines. Two received high AGREE II and AMSTAR scores. Most guidelines recommend that clinicians avoid doses greater than 90 to 200 mg of morphine equivalents per day, have additional knowledge to prescribe methadone, recognize risks of fentanyl patches, titrate cautiously, and reduce doses by at least 25% to 50% when switching opioids. Guidelines also agree that opioid risk assessment tools, written treatment agreements, and urine drug testing can mitigate risks. Most recommendations are supported by observational data or expert consensus.

Limitation: Exclusion of non–English-language guidelines and reliance on published information.

Conclusion: Despite limited evidence and variable development methods, recent guidelines on chronic pain agree on several opioid risk mitigation strategies, including upper dosing thresholds; cautions with certain medications; attention to drug–drug and drug–disease interactions; and use of risk assessment tools, treatment agreements, and urine drug testing. Future research should directly examine the effectiveness of opioid risk mitigation strategies.

Primary Funding Source: California Department of Industrial Relations and California Commission on Health and Safety and Workers' Compensation.

Ann Intern Med. 2014;160:38-47. www.annals.org

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This article was published online first at www.annals.org on 12 November 2013.

Across the United States, opioid-related overdoses have been implicated in increasing numbers of emergency department visits, hospitalizations, and deaths. Annual fatalities associated with prescription opioids increased from 4000 in 1999 to nearly 14 000 by 2006 (1). Several factors may explain these trends. First, over the past several decades, the number of patients receiving opioids and the number of doses prescribed have increased dramatically (2–4). Treating chronic pain with opioids went from being largely discouraged to being included in standards of care (2, 5, 6), and titrating doses until patients self-report adequate control has become common practice (5, 7). Today, 8% to 30% of patients with chronic noncancer pain receive opioids, with average doses typically ranging from 13 to 128 mg of morphine equivalents daily; some receive much higher doses (8). Second, the public seems to consider prescription opioids safer to abuse than illicit drugs, influencing patterns of overdose deaths (9, 10). Third, common drug–drug and drug–disease interactions contribute to overdoses. Half of fatal opioid overdoses involve the concomitant use of sedative-hypnotics, particularly benzodiazepines (1).

Given current rates of opioid overdose, policymakers are seeking solutions and standards of care are again evolving. The White House has issued action items, and an Institute of Medicine (IOM) report provides recommendations for policy audiences (11, 12). High-quality clinical practice guidelines would assist clinicians in making informed prescribing decisions and would mitigate the risks associated with using opioids. The objective of the current study was to systematically search for and evaluate the quality of guidelines addressing the use of opioids for chronic pain. A secondary objective was to compare guidelines' recommendations related to mitigating the risk for accidental overdose and misuse, including considering the quality of the evidence that guidelines provide in support of their recommendations.

See also:

Web-Only
Supplement
CME quiz

Methods

Study steps included searching for guidelines, applying selection criteria, assessing guideline quality, and extracting relevant content.

Data Sources and Searches

We searched for guidelines addressing the use of opioids in the treatment of chronic pain, which is generally defined as pain that persists beyond normal tissue healing time, assumed to be 3 months (13, 14). The long-term use of opioids has been variably defined as use for 3 to 6 months or longer (14, 15).

Information sources included MEDLINE via PubMed, the National Guideline Clearinghouse, 12 Web sites of relevant specialty societies listed on the American Medical Association Web site (16), Web sites of selected state workers' compensation agencies (17–19), and 12 international search engines (20–31) (**Appendix Figure**, available at www.annals.org). The search was last updated in July 2013.

Search terms included "opioid," "opiate," "narcotic," "chronic pain," and "pain management." For the National Guideline Clearinghouse, names of specific opioids were also used. For PubMed, "narcotic" was omitted (all results addressed substance abuse); this search was limited to documents published after 31 December 2006 because selection criteria included recent updating.

Guideline Selection

We selected English-language documents meeting the following definition: "Clinical practice guidelines are statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options" (32). Guidelines had to have been published after 2006 because half of guidelines can be outdated after 5 to 6 years (33).

Because we sought to evaluate guidelines that address the use of opioids for chronic pain in adults in general, we excluded guidelines focusing on specific conditions (for example, low back pain or cancer), populations (for example, pediatric patients or homeless persons), types of pain (for example, neuropathic pain or postoperative pain), or settings (for example, long-term care). We excluded guidelines derived entirely from another guideline and those for which we could not identify detailed information on development. Two reviewers applied criteria independently and reached agreement; a third reviewer was available to resolve disputes.

Guideline Quality Assessment

We evaluated guideline quality by using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument (34–36) and the systematic review supporting each guideline by using A Measurement Tool to Assess Systematic Reviews (AMSTAR) (37).

AGREE II

With AGREE II, appraisers rate 23 items across 6 domains (from 1 [strongly disagree] to 7 [strongly agree]), rate the overall quality of each guideline (1 to 7) and recommend for or against use. Scaled domain scores (0% to 100%) are based on the sum of ratings across all appraisers and the difference between the maximum and minimum possible scores (38).

The guidelines were rated by 4 to 6 appraisers, including 5 clinician investigators (2 of whom had limited availability) and 1 trained graduate student. One author who was also the author of a guideline (13) provided general input on content and methods but played no role in appraisals.

AMSTAR

In the original version of AMSTAR, appraisers answer 6 domain questions (yes, no, can't answer, or not applicable). Each domain question typically addresses multiple concepts. For example, 1 question states that "At least two electronic sources should be searched [concept 1] . . . Key words and/or MeSH terms must be stated [concept 2] . . . " (37).

Because including multiple concepts could lead to inconsistent scoring of "yes" or "no" responses, we modified AMSTAR by dividing the original domain questions into separate subquestions addressing single concepts (**Supplement**, available at www.annals.org). Appraisers scored each subquestion (yes, no, can't answer, or not applicable), each of the 6 domains overall (poor, fair, good, excellent, or outstanding), and the overall quality of the review (same categories as for the domains). Four to 5 appraisers rated each review individually and then met to discuss ratings and reach agreement.

Guideline Synthesis and Analysis

Three appraisers abstracted recommendations from each guideline on dosing limits, medications and formulations, titration of dose, switching from one opioid to another, drug–drug interactions, drug–disease interactions, and risk mitigation strategies (opioid risk assessment tools, written treatment agreements, and urine drug testing).

Role of the Funding Source

The Commission on Health and Safety and Workers' Compensation provided funding for this study. The funding source commissioned a synthesis of recent information on the risks and benefits of opioids for chronic pain but had no role in the design or execution of this evaluation.

RESULTS

Search and Selection of Guidelines

Of 1270 documents identified, 1132 unique records were eligible for screening, 19 full-text guidelines were considered for evaluation, and 13 were eligible (**Appendix Figure**). An online report includes a previous version of the search (39). Of 6 guidelines considered but found ineligible, 1 was derived from another guideline (18) and 5 lacked details on development methods (17, 40–43).

Table. **Selected Guideline Recommendations Related to Mitigating the Risks of Opioid Therapy During Long-Term Use for Chronic Noncancer Pain**

Recommendation	Guideline Development Group (Reference)*			
	ACOEM (55)	AGS (51, 52)	APS-AAPM (13, 57, 58)	ASIPP (49, 59)
Dose that warrants scrutiny, *mg of morphine equivalents per day*				
Most patients successfully treated with lower doses; higher doses associated with adverse effects and overdose	–	–	200†‡ (adverse effects)	90‡§ (risk for overdose)
Medications and formulations				
Methadone: risks for QTc prolongation and bioaccumulation; only experienced providers should prescribe methadone	√	√‡	√‡	√‡
Fentanyl patch: limit to opioid-tolerant patients; variable absorption, exercise, and heat increase risk for overdose	√	–	–	√‡
Immediate-release fentanyl: limit to opioid-tolerant patients; safety unknown for CNCP; risk for overdose and misuse	√	–	–	–
Meperidine: do not use for CNCP because of bioaccumulation and central nervous system toxicity	√	–	–	√‡
Codeine: ability to convert to morphine varies greatly	–	–	–	√‡
Initiation and titration of dose				
Strategies to minimize risk for overdose	Start low-dose, short-acting opioid as needed; visit in 2–3 d	Start low-dose opioid; titrate carefully; reassess often	Trial; individualize dosing§	Start low-dose, short-acting opioid; use caution
Switching between opioids				
Dose reduction: equianalgesic dosing tables omit variability	Decrease dose by 25%–50%	–	Decrease dose moderately‡	–
Switching to methadone: conversion ratios vary with dose	–	√	√‡	–
Drug–drug interactions				
Sedative-hypnotics: risk for sedation, cognitive impairment, motor vehicle accidents, and overdose	Discusses risks‡	High risk from BZDs; rarely justified	Discusses risks	If patient is receiving BZDs, opioids are contraindicated‡
Pharmacokinetic interactions: other medications affect the metabolism of specific opioids	Limited list	–	–	Many occur‖
Drug–disease interactions				
Preexisting substance abuse disorders: increased risk for overdose and misuse	√	√‡	√‡	√‖
Mood, personality, and cognitive disorders: increased risk for overdose and misuse	√	–	√‡	√‡
Sleep and obstructive pulmonary disorders: opioids exacerbate	–	–	√‡	√‡
Chronic kidney disease	–	–	Slowly increase methadone	–
Active metabolites of morphine accumulate	–	–	–	√
Screening tools for assessing risk for misuse (used in addition to patient history)				
Recommends use	√§	√‡	√‡	Consider‡‖
Provides examples	√	–	√	√
Written treatment agreements (used in addition to informed consent)				
Recommends use	√§	If concerned§	Consider‡	√‡
Provides example	√	–	√	√
Urine drug testing				
Recommends use	Baseline and at least quarterly thereafter‡	–	If risk is high; consider otherwise‡	Must use; baseline and at random thereafter‡

AAPM = American Academy of Pain Medicine; ACOEM = American College of Occupational and Environmental Medicine; AGS = American Geriatrics Society; APS = American Pain Society; ASIPP = American Society of Interventional Pain Physicians; BZD = benzodiazepine; CNCP = chronic noncancer pain; DoD = Department of Defense; DWC = Division of Workers' Compensation; ICSI = Institute for Clinical Systems Improvement; NOUGG = National Opioid Use Guideline Group; UDOH = Utah Department of Health; UMHS = University of Michigan Health System; VA = Veterans Affairs.

* Guidelines by the American Society of Anesthesiologists (53), Fine and colleagues (54), and the Work Loss Data Institute (56) are omitted. The American Society of Anesthesiologists guideline did not address topics in the table. The guideline by Fine and colleagues addressed switching from one opioid to another but not the other topics. The Work Loss Data Institute guideline content is proprietary.

† Evidence from randomized, controlled trial.

‡ Evidence from observational study.

§ Evidence from expert consensus.

‖ Evidence from another guideline.

Table—Continued

Guideline Development Group (Reference)*					
NOUGG (46, 60–62)	Colorado DWC (19)	ICSI (47)	UMHS (44)	UDOH (48, 50)	VA/DoD (45)
200†§ (adverse effects)	120‡ (adverse effects)	200‖ (adverse effects)	100	120–200‖	200§ (trials used ≤300†)
√‡	√‖	√‡	√	√	√‡
√‡	√	√‡	√	√	√
√	Never use for CNCP	Risk for fatal overdose‡	–	–	√
√‡	√	√	–	√	√
√‡	√	√	–	–	√
Start low-dose opioid; increase gradually; monitor§	Trial; visits every 2–4 wk; multidisciplinary pain management	Titrate to maximize benefits and minimize risks‖	Visits weekly to monthly§	Trial; visits every 2–4 wk‖	Titrate up no more than every 5 half-lives‡
Decrease dose by 25%–50%	–	Decrease dose by 30%‖	–	Decrease dose by 25%–50%	Decrease dose by 30%–50%
–	–	–	√‡	√	√
Try to taper BZDs‡	Avoid sedatives or use very low doses	Sedatives sometimes indicated; decrease doses	Avoid prescribing BZDs with opioids	Discusses risks	Watch for increased adverse effects‡
–	List for tramadol	Lists for several opioids	–	Look for interactions	Lists for several opioids
√‡	Comanage with addiction specialist	Comanage with addiction specialist‖	√	√	√
√‡	√‡	√	√	√	√‡
√‡	√	–	√	√	√‡
–	Consider screening	Use hydromorphone	–	–	Decrease oxymorphone
√‡	√	Morphine, codeine	–	Decrease dose	√
Consider‡	–	√‡	Consider‡	√‖	√‡
√	–	√	√	√	√
May be helpful, particularly if risk is high§	√‖	√§	Strongly consider, particularly if risk is high§	Agree on plan; signature is optional	Request that patient sign‡
√	–	√	√	√	√
If using, consider pros and cons§	Mandatory	√	Baseline and at least yearly thereafter§	Consider‖	Baseline and at random thereafter‡

Selected Guidelines

Appendix Table 1 (available at www.annals.org) lists the 13 eligible guidelines; all were published in 2009 or later. Systematic reviews were conducted in 2008 or later (among guidelines that reported this).

Seven guidelines apply broadly to adults with chronic pain (13, 44–50). Six have slightly narrower scopes: The American Geriatrics Society guideline addresses adults older than 65 years (51, 52); the American Society of Anesthesiologists guideline emphasizes procedures (53); a guideline by Fine and colleagues addresses opioid rotation (54); and guidelines from the American College of Occupational and Environmental Medicine, the Work Loss Data Institute, and the Colorado Division of Workers' Compensation consider individuals with pain due to work-related conditions (19, 55, 56).

Guideline Quality Assessment

AGREE II

Overall guideline assessment scores were 3.00 to 6.20 (**Appendix Table 2**, available at www.annals.org). Rigor-of-development scores were 20% to 84%, clarity-of-presentation scores ranged from 37% to 93%, applicability scores were 13% to 56%, and editorial independence scores ranged from 0% to 88%.

Ratings were highest for a guideline by the American Pain Society and the American Academy of Pain Medicine (APS-AAPM) (13) and one by the Canadian National Opioid Use Guideline Group (46), the only guidelines that more than 50% of appraisers voted to use without modification. Most appraisers recommended against using 4 other guidelines because of limited confidence in development methods, lack of evidence summaries, or concerns about readability (19, 44, 53, 54).

Among the low- to intermediate-quality guidelines (19, 44, 45, 47–56), shortcomings included limited or no descriptions of input from guideline end users or patients; criteria for selecting evidence, strengths and limitations of evidence, and methods for formulating recommendations; external reviews before publication; plans for updating; barriers to implementation, resource implications, and how to implement guideline recommendations; monitoring and auditing criteria; and measures taken to ensure editorial independence.

AMSTAR

Systematic reviews within 10 guidelines were of poor or fair quality (19, 44, 47–56). The APS-AAPM review was of excellent to outstanding quality, the review by the Canadian National Opioid Use Guideline Group was of good to excellent quality, and the review by the Department of Veterans Affairs and Department of Defense (VA/DoD) was of good quality (**Appendix Table 3**, available at www.annals.org) (13, 45, 46).

Reasons for lower scores included limited information about whether inclusion criteria were selected beforehand, whether at least 2 reviewers participated in study selection and data extraction, whether more than 1 database was searched, search terms used, inclusion criteria, lists of included studies, whether the scientific quality of the studies was assessed, how information from different studies was combined, and whether publication bias was considered.

Guideline Synthesis and Analysis

The **Table** compares recommendations from 10 guidelines about mitigating risks when prescribing opioids (3 guidelines had little relevant content). The APS-AAPM, Canadian National Opioid Use Guideline Group, American Society of Interventional Pain Physicians, and VA/DoD guidelines make explicit links between each recommendation and original research evidence more frequently than the other guidelines do (13, 45, 46). Among recommendations in the **Table**, only upper dosing thresholds are reported to be supported by evidence from randomized, controlled trials; others are supported by lower-quality evidence or expert opinion. Even the higher-quality guidelines typically relied on modest numbers of lower-quality observational studies for many recommendations (13, 45, 47, 57, 60). Nonetheless, many recommendations are concordant across the guidelines.

Eight guidelines concur that higher doses require caution (19, 44, 45, 47, 50, 57, 59, 60). Four consider higher doses to be 200 mg of morphine equivalents per day, on the basis of randomized, controlled trials showing that most patients achieve pain control with lower doses and observational data showing that the prevalence of adverse effects increases at higher doses (45, 47, 57, 60). Because recent observational studies detected more overdoses with doses greater than 100 mg, the American Society of Interventional Pain Physicians guideline (2012) recommends staying below 90 mg unless pain is intractable (49, 59). The University of Michigan Health System guideline (2012) advises that patients receiving more than 100 mg be treated by pain specialists (44).

Ten guidelines—6 of which cite observational data—agree that methadone poses risks for dose-related QTc prolongation and respiratory suppression due to a long half-life and unique pharmacokinetics (13, 19, 44–47, 49, 50, 52, 55, 57, 60). These guidelines generally recommend that only knowledgeable providers prescribe methadone. Eight guidelines recommend caution with the fentanyl patch, including limiting use to opioid-tolerant patients and being aware that unpredictable absorption can occur with fever, exercise, or exposure to heat (19, 44, 45, 47, 49, 50, 55, 60, 61). Cited evidence includes an observational study investigating fentanyl overdoses in Ontario, Canada, as well as case reports submitted to the U.S. Food and Drug Administration (47, 49, 60, 63).

Ten guidelines make variable consensus-based statements about initiating and titrating opioids, such as using a trial period, individualizing therapy, engaging multidisciplinary pain management teams, increasing doses slowly,

and scheduling regular follow-up visits (13, 19, 44–48, 50, 52, 55, 59).

Regarding switching from one opioid to another, 7 guidelines agree that reducing doses by at least 25% to 50% is necessary to avoid inadvertent overdose; the guideline by Fine and colleagues provides nuanced recommendations (13, 45, 47, 48, 50, 54, 55, 60). Two guidelines cite a systematic review of observational studies, which found that patients respond variably to different drugs (13, 54). Five guidelines mention that many persons of Caucasian or Chinese ancestry cannot metabolize codeine to morphine and are therefore less responsive to its analgesic effects and cannot develop tolerance (19, 45, 47, 59–61). Conversely, 5 guidelines note that some patients metabolize codeine to morphine ultra-rapidly, potentially resulting in overdose (19, 47, 49, 59, 60); certain ethnicities are at greater risk, particularly persons from North Africa and the Middle East (45).

Ten guidelines concur, on the basis of observational data, that benzodiazepines and opioids are a high-risk combination, particularly in elderly adults (13, 19, 44, 45, 47, 48, 50, 52, 55, 59–61). Five recommend against prescribing both together unless clearly indicated (19, 44, 49, 52, 60, 61). Six guidelines describe pharmacokinetic interactions between other medications and opioids, particularly methadone, fentanyl, oxycodone, and tramadol (19, 45, 47–49, 55). Six guidelines mention the accumulation of active, toxic metabolites of morphine among patients with kidney disease (19, 45, 47, 49, 50, 60). Ten guidelines consider the leading risk factors for overdose or misuse as having a personal or family history of substance abuse and having psychiatric issues (13, 44, 45, 47–49, 52, 55, 59–61); 3 cite observational studies (13, 52, 60, 61). Seven guidelines identify obstructive respiratory disorders as risk factors for overdose, also on the basis of observational data (13, 19, 44, 45, 48, 50, 59–61).

In terms of mitigating risks, the evidence for opioid risk assessment tools, treatment agreements ("contracts"), and urine drug testing is weak, but recommendations vary in strength from "may consider" to "must." Nine guidelines recommend considering or using opioid risk assessment tools and treatment agreements on the basis of observational studies and expert consensus (13, 44, 45, 47, 48, 50, 52, 55, 59–61). Eight guidelines mention or provide specific risk assessment instruments for use when initiating therapy with long-term opioids, such as the Screener and Opioid Assessment for Patients with Pain (SOAPP), version 1 (64); the revised SOAPP (65); and the Opioid Risk Tool, or monitoring tools for use during follow-up, including the Pain Assessment and Documentation Tool (66, 67) and the Current Opioid Misuse Measure (44, 45, 47–50, 55, 57, 60, 68). For detecting aberrant drug-related behaviors, the self-administered SOAPP, version 1, and the Current Opioid Misuse Measure performed well in higher-quality observational studies (57). Treatment agreements may improve adherence and providers' willingness to prescribe opioids, on the basis of a few small, observational studies (49, 57, 60).

Nine guidelines find urine drug testing to be helpful, but recommendations vary (13, 19, 44, 45, 47, 48, 55, 59, 60). Two recommend mandatory testing for all patients (19, 49), another advises testing for patients at higher risk for substance abuse disorders (13), and 2 comment that screening low-risk populations increases false-positive results and is less cost-effective (13, 60, 61). False-negative results can occur because a common test, the enzyme-linked immunoassay, does not consistently detect hydrocodone, fentanyl, hydromorphone, oxycodone, methadone, or certain benzodiazepines; gas chromatography or mass spectrometry will identify specific substances when requested (44, 46, 50, 60–62). Nonadherence, diversion, tampering, and lactic acidosis can also cause unexpected negative results. The differential for unexpected positive results includes abuse, consulting multiple physicians, self-treatment of uncontrolled pain, interference by other medications, eating poppy seeds, and laboratory error (13, 44, 46, 49, 59–62).

Discussion

Increasing overdoses on prescription opioids have prompted efforts to redefine standards of care, particularly for patients with chronic pain, who may be prescribed opioids for long-term use. We evaluated the quality of 13 guidelines on using opioids to treat chronic pain and compared recommendations related to mitigating risks for overdose and misuse. Two guidelines received high ratings: one by APS-AAPM (13) and another by the Canadian National Opioid Use Guideline Group (46). Both apply to a broad range of adults, were developed using comprehensive systematic reviews and rigorous methods for formulating recommendations, and frequently link recommendations to evidence. Our appraisers found 7 other guidelines to be of intermediate quality and recommended against using the remaining 4. Systematic reviews supporting 10 guidelines were judged, on the basis of publicly available information, to be of poor to fair quality.

Although the guidelines involve varied development methods and clinical emphases, a consensus has emerged across them on several issues. They generally agree about the need for caution in prescribing doses greater than 90 to 200 mg of morphine equivalents per day, having knowledgeable clinicians manage methadone, recognizing risks associated with fentanyl patches, titrating with caution, and reducing doses by at least 25% to 50% when switching from one opioid to another. They also agree that opioid risk assessment tools, written treatment agreements, and urine drug testing can be helpful when opioids are prescribed for long-term use. Recommendations from earlier guidelines are generally similar to those published recently. Most of these recommendations are based on epidemiologic and observational studies showing associations be-

tween certain exposures, such as drugs or doses, and greater risks for overdose or misuse. Few studies seem to have directly addressed questions of whether changing practice decreases risk. Given the pressing need to address opioid-related adverse outcomes, which some have described as an epidemic (69), developers seem to agree on forging recommendations based on relatively weak or indirect evidence now rather than waiting for more rigorous studies.

It may be unusual for multiple guidelines to make such similar recommendations, but the variability in guideline quality that we observed is not. For example, among 19 breast cancer guidelines, AGREE II rigor-of-development scores were 16.7% to 89.6%, clarity-of-presentation scores ranged from 52.8% to 94.4%, applicability scores were 6.3% to 83.6%, and editorial independence scores ranged from 12.5% to 79.2% (70). Among 3 migraine guidelines, AGREE II rigor-of-development scores were 35% to 93%, clarity-of-presentation scores ranged from 6% to 92%, applicability scores were 20% to 88%, and editorial independence scores ranged from 29% to 86%; overall scores were 2 to 6, and appraisers recommended against using 1 guideline (71). Among 11 mammography guidelines evaluated using the original AGREE instrument and AMSTAR, appraisers recommended against implementing 5 guidelines, and 5 systematic reviews performed poorly (72).

Compared with these previous guidelines, the current opioid guidelines received lower scores on "applicability": None scored higher than 56%. Applicability includes consideration of potential barriers to and facilitators of implementation, strategies to improve uptake by providers, and resource implications of applying the guideline. Barriers to implementation are a major reason that physicians are often slow to incorporate clinical guidelines into their decision making (73). To identify such barriers, guideline developers and implementers are starting to use the GuideLine Implementability Appraisal (GLIA) tool (74–76), which assesses "executability" (know what to do), "decidability" (can tell when to do it), validity, flexibility, effect on process of care, measurability, novelty or innovation, and "computability" (can be operationalized in an electronic health record system) (77). Although GLIA is labor-intensive (76), it probably requires fewer resources than pilot testing and is preferable to issuing a guideline that is not used. Developers of opioid guidelines could incorporate GLIA into the next updating process, thereby improving applicability.

Although we selected guidelines that had been updated within the past 6 years, some evidence has already started to change, particularly regarding the risk for overdose. Five guidelines published before 2012 consider doses greater than 200 mg of morphine equivalents per day to confer higher risk. Three observational studies from 2010 and 2011 show that, compared with patients receiving no more than 20 mg, the risk for serious or fatal overdose increases 1.9- to 3.1-fold with doses of 50 to 100 mg and increases dramatically with doses greater than 100 to 200 mg (78–80). Guidelines published in 2012 use thresholds of 90 to 100 mg. In 2007, the state of Washington implemented workers' compensation guidelines recommending evaluation by a pain management expert for patients receiving more than 120 mg/d as well as other risk mitigation strategies that are similar to or, in some areas, more restrictive than those of the guidelines reviewed here. Although pain control has not been described, the number of patients receiving opioids and the doses prescribed started decreasing in 2007 and fatal overdoses decreased in 2010 (4).

Given that overdoses occur even at lower doses, some may wonder about the overall risks and benefits of using opioids for chronic pain. According to previous systematic reviews of randomized, controlled trials, oral opioids are substantially more effective than placebo or nonsteroidal agents, with 30% to 50% decreases in pain severity and significant improvements in functional status (14, 81–83). However, study quality has not been high, and the duration of follow-up has often been limited (14, 84). At least one third of patients stop opioid use because of adverse effects (46, 81, 82, 85). Abuse occurs in 0.43% to 3.27% of patients and addiction affects 0.042%, but 11.5% engage in aberrant drug-related behaviors or illicit use (14, 85, 86). This evidence has generally been incorporated into the guidelines and is reflected in the supportive but cautious approach that they take toward long-term opioid therapy.

Our evaluation has several limitations. First, we relied on publicly available information, so we were unable to evaluate several guidelines (17, 40–43, 87) or the clarity of the proprietary Work Loss Data Institute guideline. Although AGREE scores can improve when developers provide supplemental information (88), the IOM recently outlined guideline development standards stating, "The processes by which a [clinical practice guideline] is developed and funded should be detailed explicitly and publicly accessible" (32). Second, neither the IOM nor AGREE stipulate how guidelines should select topics. To be useful, guidelines should address the challenges that clinicians face in practice, but developers may exclude clinically important topics when available evidence does not meet minimum standards.

In conclusion, rigorous clinical practice guidelines could help providers to attenuate the increasing rates of opioid misuse and overdose among patients with chronic pain. Recent guidelines make similar recommendations about strategies for reducing these risks despite variability in development methods, suggesting a clinical consensus for practices that could be adopted until more evidence becomes available. They agree on using upper dosing thresholds; cautions with certain medications; attention to drug–drug and drug–disease interactions; and risk assessment tools, treatment agreements, and urine drug testing. Although such recommendations can guide practice now,

future research should directly examine the effectiveness of opioid risk mitigation strategies, including effects on pain control and overdose rates.

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Financial Support: By the California Department of Industrial Relations and the California Commission on Health and Safety and Workers' Compensation. Dr. Nuckols was supported by a Mentored Clinical Scientist Career Development Award (K08) from the Agency for Healthcare Research and Quality (grant HS17954).

Potential Conflicts of Interest: Dr. Nuckols: *Other:* California Commission on Health and Safety and Worker's Compensation, Collaborative Spine Research Foundation. Dr. Chou: *Grant:* California Commission on Health and Safety and Worker's Compensation, American Pain Society. All other authors have no disclosures. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M13-1193.

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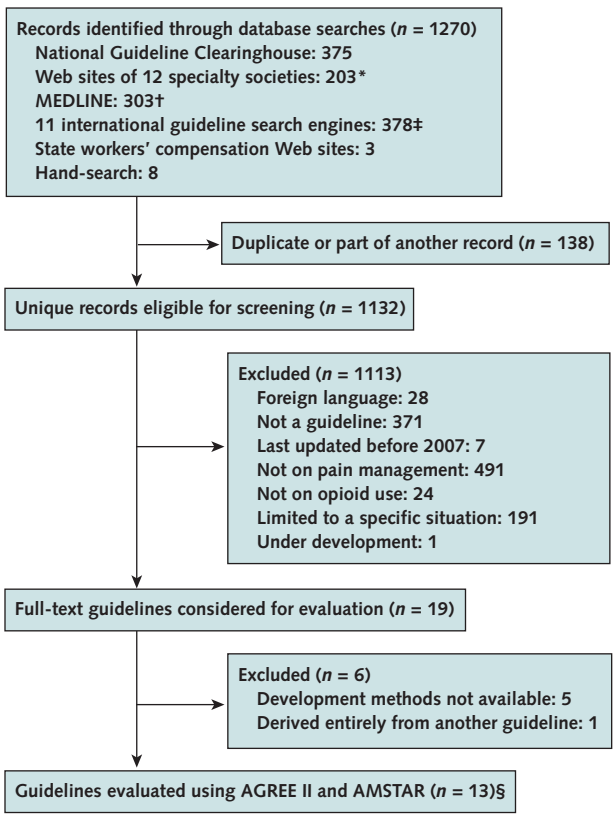
Appendix Figure. **Summary of evidence search and selection.**



AGREE II = Appraisal of Guidelines for Research and Evaluation II; AMSTAR = A Measurement Tool to Assess Systematic Reviews.

* Includes the American Academy of Family Physicians, American Academy of Pain Medicine, American Academy of Physical Medicine and Rehabilitation, American College of Occupational and Environmental Medicine, American College of Physicians, American Geriatrics Society, American Society of Addiction Medicine, American Society of Anesthesiologists, American Society of Interventional Pain Physicians, Association of Military Surgeons of the United States, National Medical Association, and Society of Medical Consultants to the Armed Forces.

† The exact PubMed search terms were "analgesics, opioid"[MeSH], "opioid"[tiab], "opioids"[tiab], "opioid analgesic"[tiab], "opioid analgesics"[tiab], "opiate"[tiab], "opiates"[tiab], "chronic pain"[MeSH], "chronic pain"[tiab], "pain management"[MeSH], and "pain management"[tiab] combined with "guideline"[Publication Type], "guideline*"[tiab], "position statement*"[tiab], "practice parameter*"[tiab], "position paper*"[tiab], and "consensus statement*"[tiab].

‡ Includes the Guidelines International Network; National Institute for Health and Care Excellence; Canadian Medical Association Infobase: Clinical Practice Guidelines; Clinical Practice Guidelines Portal of the Australian Government; Scottish Intercollegiate Guidelines Network; New Zealand Guidelines Group; Biblioteca de Guías de Práctica Clínica del Sistema Nacional de Salud (Library of Clinical Practice Guidelines from the Spanish National Health System); German Agency for Quality in Medicine; German National Disease Management Guidelines Programme: German Disease Management Guidelines; British Columbia Ministry of Health; and Australian Government National Health and Medical Research Council: Guidelines and Publications.

§ The American Geriatrics Society updated its guideline in 2009 and stated that the 2002 guideline, which covers slightly different material, was still up to date. When counting guidelines, we considered these to be components of 1 document.

Appendix Table 1. **Guidelines Meeting All Selection Criteria and Included in Quality Appraisal**

Guideline	Development Group	Guideline Last Reviewed	Systematic Review Updated	Reference
ACOEM Guidelines for Chronic Use of Opioids	ACOEM	2011	References to primary literature dated 2007 or earlier*	55
Pharmacological Management of Persistent Pain in Older Persons	AGS Panel on Pharmacological Management of Persistent Pain in Older Persons	2009	References to primary literature dated 2008 or earlier	52
The Management of Persistent Pain in Older Persons	AGS Panel on Persistent Pain in Older Persons	2009	–	51
Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain	APS-AAPM	2009	October 2008	13, 57, 58
Practice Guidelines for Chronic Pain Management: An Updated Report by the American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine	ASA	2010	2009	53
American Society of Interventional Pain Physicians (ASIPP) Guidelines for Responsible Opioid Prescribing in Chronic Non-Cancer Pain	ASIPP	2012	References to primary literature dated 2012 or earlier	49, 59
Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain	NOUGG	2010	July 2009	46, 60–62
Chronic Pain Disorder Medical Treatment Guidelines	Colorado DWC	2011	November 2011	19
Establishing "Best Practices" for Opioid Rotation: Conclusions of an Expert Panel	Department of Pain Medicine and Palliative Care, Beth Israel Medical Center and Department of Anesthesiology, Pain Research Center, University of Utah School of Medicine	2009	References to primary literature dated 2007 or earlier	54
Assessment and Management of Chronic Pain	ICSI	2011	August 2011	47
Managing Chronic Non-Terminal Pain in Adults, Including Prescribing Controlled Substances	UMHS	2012	January 2010	44
Utah Clinical Guidelines on Prescribing Opioids for Treatment of Pain	UDOH	2009	References to primary literature dated 2007 or earlier	48, 50
Clinical Practice Guideline for Management of Opioid Therapy for Chronic Pain	VA/DoD	2010	March 2009	45
Pain (Chronic)†	WLDI	2011	Not reported (no references)	56

AAPM = American Academy of Pain Medicine; ACOEM = American College of Occupational and Environmental Medicine; AGS = American Geriatrics Society; APS = American Pain Society; ASA = American Society of Anesthesiologists; ASIPP = American Society of Interventional Pain Physicians; DoD = Department of Defense; DWC = Division of Workers' Compensation; ICSI = Institute for Clinical Systems Improvement; NOUGG = National Opioid Use Guideline Group; UDOH = Utah Department of Health; UMHS = University of Michigan Health System; VA = Veterans Affairs; WLDI = Work Loss Data Institute.

* Excludes such sources as references to other guidelines, narrative and systematic reviews, government reports, and book chapters because these are often identified through means other than systematic reviews of the literature.

† From *The Official Disability Guidelines* product line (including *ODG Treatment in Workers Comp*), which is updated annually.

Appendix Table 2. Results of AGREE II Evaluation

Variable	Guideline Development Group (Reference)													Mean (Range), %
	ACOEM (55)	AGS (51, 52)	APS-AAPM (13, 57, 58)	ASA (53)	ASIPP (49, 59)	NOUGG (46, 60–62)	Colorado DWC (19)	Fine et al (54)	ICSI (47)	UMHS (44)	UDOH (48, 50)	VA/DoD (45)	WLDI (56)	
AGREE II domain score, %														
Scope and purpose (the overall aim of the guideline, the specific health questions, and the target population)	78	68	89	72	85	76	53	39	86	51	49	88	69	69 (39–89)
Stakeholder involvement (the extent to which the guideline was developed by the appropriate stakeholders and represents the views of its intended users)	55	39	73	43	53	77	41	23	69	39	50	58	59	52 (23–77)
Rigor of development (the process used to gather and synthesize the evidence and the methods used to formulate and update the recommendations)	60	44	84	33	56	74	27	24	56	20	43	55	49	48 (20–84)
Clarity of presentation (the language, structure, and format of the guideline)	67	68	84	54	79	93	37	71	80	64	74	78	–*	71 (37–93)
Applicability (the likely barriers to and facilitators of implementation, strategies to improve uptake, and resource implications of applying the guideline)	55	30	41	21	40	56	13	28	41	46	42	42	31	37 (13–56)
Editorial independence (the influence of the funding body on development and disclosure of conflicts of interest)	75	63	88	2	69	56	0	23	52	37	48	8	50	44 (0–88)
Mean domain score	63	49	76	38	61	73	29	33	62	39	49	57	51	52 (28–76)
Overall outcome of guideline development														
Mean overall quality score	4.75	4.00	6.20	3.00	4.67	6.00	3.00	3.40	4.50	3.60	3.60	4.75	3.50	4.23 (3.00–6.20)
Votes to recommend use														
Yes, *n (%)*	2 (50)	1 (20)	5 (100)	0	1 (17)	3 (75)	0	1 (20)	2 (40)	0	0	1 (25)	–*	–
Yes, with modifications, *n (%)*	0	4 (80)	0	0	4 (67)	1 (25)	2 (40)	1 (20)	2 (40)	1 (20)	3 (60)	3 (75)	–*	–
No, *n (%)*	2 (50)	0	0	4 (100)	1 (17)	0	3 (60)	3 (60)	1 (20)	4 (80)	2 (40)	0	–*	–
Total votes, *n*	4	5	5	4	6	4	5	5	5	5	5	4	–*	–

AAPM = American Academy of Pain Medicine; ACOEM = American College of Occupational and Environmental Medicine; AGREE II = Appraisal of Guidelines for Research and Evaluation II; AGS = American Geriatrics Society; APS = American Pain Society; ASA = American Society of Anesthesiologists; ASIPP = American Society of Interventional Pain Physicians; DoD = Department of Defense; DWC = Division of Workers' Compensation; ICSI = Institute for Clinical Systems Improvement; NOUGG = National Opioid Use Guideline Group; UDOH = Utah Department of Health; UMHS = University of Michigan Health System; VA = Veterans Affairs; WLDI = Work Loss Data Institute.

* The guideline is proprietary and text was unavailable, so raters could not assess clarity of presentation or decide whether to recommend use. Domain ratings were based on information the developer has made public about development methods and information related to the other domains.

Appendix Table 3. Results of AMSTAR Evaluation

Question	Guideline Development Group (Reference)												
	ACOEM (55)	AGS (51, 52)	APS-AAPM (13, 57, 58)	ASA (53)	ASIPP (49, 59)	NOUGG (46, 60–62)	Colorado DWC (19)	Fine et al (54)	ICSI (47)	UMHS (44)	UDOH (48, 50)	VA/DoD (45)	WLDI (56)
Was an "a priori" design provided?	F	F	O	F	F	E	P	F	F	G	F	G	G
Was there duplicate study selection and data extraction?	F	P	O	P	P	G	P	P	P	P	P	P	P
Was a comprehensive literature search performed?	G	P	E	P	F	O	F	P	F	F	G	G	G
Was the status of publication (e.g., gray literature) used as an inclusion criterion?	G	F	G	F	F	G	P	P	F	G	F	G	G
Was a list of studies (included and excluded) provided?	P	P	E	F	F	G	F	P	P	P	F	F	P
Were the characteristics of the included studies provided?	P	P	O	P	P	G	F	P	P	P	P	P	P
Was the scientific quality of the included studies assessed and documented?	F	F	E	P	P	G	G	P	F	P	F	G	G
Was the scientific quality of the included studies used appropriately in formulating conclusions?	G	G	O	F	G	G	F	P	F	P	P	E	F
Were the methods used to combine the findings of studies appropriate?	F	F	E	F	F	E	P	P	P	P	P	G	F
Was the likelihood of publication bias assessed?	P	P	P	F	P	G	P	P	P	P	P	P	P
Was the conflict of interest stated?	F	F	O	P	F	F	F	F	P	F	F	F	P
Overall rating	F	P–F	E–O	P–F	F	G–E	P–F	P	P–F	P–F	F	G	F–G

AAPM = American Academy of Pain Medicine; ACOEM = American College of Occupational and Environmental Medicine; AGS = American Geriatrics Society; AMSTAR = A Measurement Tool to Assess Systematic Reviews; APS = American Pain Society; ASA = American Society of Anesthesiologists; ASIPP = American Society of Interventional Pain Physicians; DoD = Department of Defense; DWC = Division of Workers' Compensation; E = excellent; F = fair; G = good; ICSI = Institute for Clinical Systems Improvement; NOUGG = National Opioid Use Guideline Group; O = outstanding; P = poor; UDOH = Utah Department of Health; UMHS = University of Michigan Health System; VA = Veterans Affairs; WLDI = Work Loss Data Institute.