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WRITTEN STATEMENT OF G. CALEB ALEXANDER, MD, MS
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BEFORE THE SENATE VETERANS' AFFAIRS COMMITTEE
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Good morning Chairman Isakson, Ranking Member Blumenthal and Members of the Committee. Thank you for the opportunity to speak today.

I am a practicing internist and prescription drug expert at the Johns Hopkins Bloomberg School of Public Health, where I co-direct the Johns Hopkins Center for Drug Safety and Effectiveness. The opinions expressed herein are my own and do not necessarily reflect the views of Johns Hopkins University.

Doctors of my generation were taught not to worry about the addictive potential of opioids if a patient had true pain. Although well intentioned, many doctors have unwittingly contributed to soaring opioid use . . . so much so that enough opioids are prescribed each year to provide every adult in the United States a 4-week round the clock supply of Vicodin.

I know that you are well aware of the devastating consequences of this epidemic on America's families. We have lost far too many lives – more than *twice* the number of Americans as have died in the Vietnam, Iraq and Afghanistan wars combined – and these deaths are the tip of the iceberg. Although there are many contributors to this epidemic, a core problem is that doctors and patients continue to overestimate the benefits of opioids and underestimate their risks.

In my testimony, I would like to mention three important steps to address this problem. I will also discuss several popular ideas that I am concerned may take our eyes off the ball.

First, we need to continue to improve prescribing practices. Best practices for opioid use have been described – including cautious use with longer durations or higher doses, limiting the use of fentanyl patches and methadone for pain, incorporating multidisciplinary pain management teams, and avoiding the combination of opioids with medicines such as benzodiazepines. These approaches are especially vital among patients with comorbid conditions such as mood disorders, posttraumatic stress disorder (PTSD), traumatic brain injury (TBI) or substance use, since high-risk opioid use and adverse outcomes are both more common among these patients.

To improve practices, it is also vital that we continue to improve the measurement and accessibility of data about opioid utilization and prescribing at a patient, provider, clinic and health system level. Such measurements allow for benchmarking and enhance our understanding of practices contributing to opioid misuse and overdose deaths.

Second, we need to help people who are addicted to opiates access effective treatment. Treatment with the medicines buprenorphine and methadone is the most effective means of helping individuals regain control of their lives and avoid death by overdose, yet despite over 5 million Americans with opioid dependence, fewer than 1 in 5 are receiving available treatments due to low provider interest and a variety of regulatory and payment barriers.

Third, we need to vastly expand opportunities for people to get rid of opiates that they do not need. It is stunning that these drugs are so easy to get, yet so difficult to get rid of. There are literally millions of pounds of unwanted and unused medicines sitting in kitchen drawers, bathroom cabinets and bedroom nightstands all over America. The DEA recently finalized its rules regarding the disposal of controlled substances, and properly implemented, I believe that these "take back" programs can serve an important role in reducing opioid-related injuries and deaths.

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Other risk mitigation methods such as patient contracts, risk assessment tools and urine testing are increasingly common. Despite their appeal, the scientific evidence to support them is limited. Although some of these approaches, such as urine testing, may be reasonable to routinely implement in clinical practice, such measures do not reduce the addictive potential of these products, nor do they change the overall unfavorable risk/benefit balance of them for many current opioid recipients.

The FDA and manufacturers are also pursuing so-called “abuse deterrent formulations” to reduce the chance a particular product will be misused. These formulations should also be regarded with caution. While these re-engineered medicines are designed to thwart abuse, their active products are no less addictive, and most individuals who abuse or are addicted to opioids swallow them whole. Moreover, our research suggests that prescribers may have important misconceptions regarding their safety. In short, I am not convinced that we can engineer our way out of this problem.

Some have framed efforts to reign in runaway prescribing as a threat to quality of care for those with chronic pain. As a practicing physician, I can assure you, nothing could be further from the truth. An overwhelming amount of evidence supports the compatibility of effective pain treatment with reducing opioid prescribing. High quality care for patients in pain isn’t jeopardized by such efforts, it demands it.

Thank you for the opportunity to testify today. I look forward to your questions.

The Prescription Opioid and Heroin Crisis: A Public Health Approach to an Epidemic of Addiction

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Abstract

Public health authorities have described, with growing alarm, an unprecedented increase in morbidity and mortality associated with use of opioid pain relievers (OPRs). Efforts to address the opioid crisis have focused mainly on reducing nonmedical OPR use. Too often overlooked, however, is the need for preventing and treating opioid addiction, which occurs in both medical and nonmedical OPR users. Overprescribing of OPRs has led to a sharp increase in the prevalence of opioid addiction, which in turn has been associated with a rise in overdose deaths and heroin use. A multifaceted public health approach that utilizes primary, secondary, and tertiary opioid addiction prevention strategies is required to effectively reduce opioid-related morbidity and mortality. We describe the scope of this public health crisis, its historical context, contributing factors, and lines of evidence indicating the role of addiction in exacerbating morbidity and mortality, and we provide a framework for interventions to address the epidemic of opioid addiction.

INTRODUCTION

Over the past 15 years, the rate of opioid pain reliever (OPR) use in the United States has soared. From 1999 to 2011, consumption of hydrocodone more than doubled and consumption of oxycodone increased by nearly 500% (42). During the same time frame, the OPR-related overdose death rate nearly quadrupled (15). According to the United States Centers for Disease Control and Prevention (CDC), the unprecedented increase in OPR consumption has led to the "worst drug overdose epidemic in [US] history" (58). Given the magnitude of the problem, in 2014 the CDC added opioid overdose prevention to its list of top five public health challenges (13).

Overdose mortality is not the only adverse public health outcome associated with increased OPR use. The rise in opioid consumption has also been associated with a sharp increase in emergency room visits for nonmedical OPR use (69) and in neonatal abstinence syndrome (57). Moreover, from 1997 to 2011, there was a 900% increase in individuals seeking treatment for addiction to OPRs (66, 68). The correlation between opioid sales, OPR-related overdose deaths, and treatment seeking for opioid addiction is striking (**Figure 1**).

Addiction is defined as continued use of a drug despite negative consequences (1). Opioids are highly addictive because they induce euphoria (positive reinforcement) and cessation of chronic use produces dysphoria (negative reinforcement). Chronic exposure to opioids results in structural and functional changes in regions of the brain that mediate affect, impulse, reward, and motivation (83, 91). The disease of opioid addiction arises from repeated exposure to opioids and can occur in individuals using opioids to relieve pain and in nonmedical users.

Another important feature of the opioid addiction epidemic is the relationship between OPR use and heroin use. According to the federal government's National Survey on Drug Use and Health (NSDUH), 4 out of 5 current heroin users report that their opioid use began with OPRs (54). Many of these individuals appear to be switching to heroin after becoming addicted to OPRs because heroin is less expensive on the black market. For example, in a recent sample of

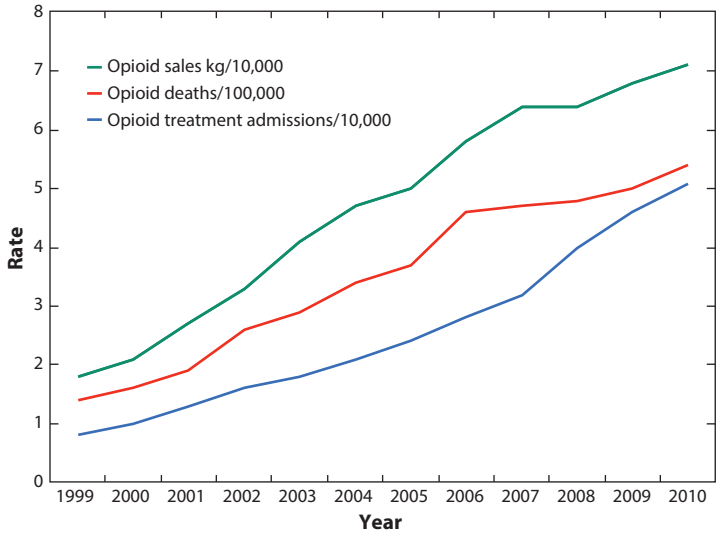

Figure 1

Rates of OPR sales, OPR-related unintentional overdose deaths, and OPR addiction treatment admissions, 1999–2010. Abbreviation: OPR, opioid pain reliever. Source: 10.

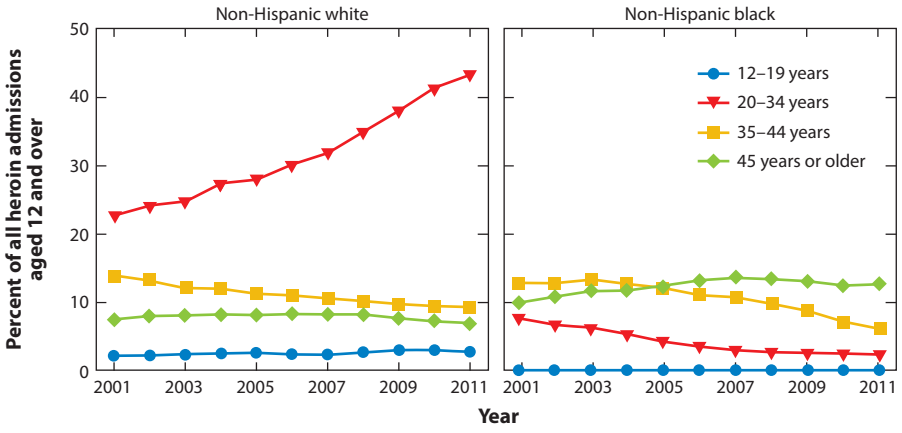

Figure 2

Heroin admissions, by age group and race/ethnicity: 2001–2011. Source: 68.

opioid-addicted individuals who switched from OPRs to heroin, 94% reported doing so because OPRs "were far more expensive and harder to obtain" (16, p. 24).

The increased prevalence of opioid addiction has also been associated with increases in heroin-related morbidity and mortality. For example, since 2001, heroin addiction treatment admissions for whites ages 20–34 have increased sharply (**Figure 2**). During this time frame, heroin overdose deaths among whites ages 18–44 increased by 171% (14).

HISTORY OF OPIOID ADDICTION IN THE UNITED STATES

The current opioid addiction crisis is, in many ways, a replay of history. America's first epidemic of opioid addiction occurred in the second half of the nineteenth century. In the 1840s, the estimated national supply of opium and morphine could have supported a maximum of 0.72 opioid-addicted individuals per 1,000 persons (18). Over the next 50 years, opioid consumption soared by 538%. It reached its peak in the mid-1890s, when the supply could have supported a maximum of ~4.59 opioid-addicted individuals per 1,000 persons. The ceiling rate then began to decline, and by 1920 there were no more than 1.97 opioid-addicted individuals per 1,000 persons in the United States.

The epidemic had diverse origins. Mothers dosed themselves and their children with opium tinctures and patent medicines. Soldiers used opium and morphine to treat diarrhea and painful injuries. Drinkers alleviated hangovers with opioids. Chinese immigrants smoked opium, a practice that spread to the white underworld. But the main source of the epidemic was iatrogenic morphine addiction, which coincided with the spread of hypodermic medication during 1870–1895. The model opioid-addicted individual was a native-born white woman with a painful disorder, often of a chronic nature.

Nineteenth-century physicians addicted patients—and, not infrequently, themselves—because they had few alternatives to symptomatic treatment. Cures were scarce and the etiology of painful conditions was poorly understood. An injection of morphine almost magically alleviated symptoms, pleasing doctors and patients. Many patients continued to acquire and inject morphine, the sale of which was poorly controlled.

The revolutions in bacteriology and public health, which reduced diarrheal and other diseases commonly treated with opium; the development of alternative analgesics such as aspirin; stricter

prescription laws; and admonitions about morphine in the lay and professional literature stemmed the addiction tide. One important lesson of the first narcotic epidemic is that physicians were educable. Indeed, by 1919, narcotic overprescribing was the hallmark of older, less-competent physicians. The younger, better-trained practitioners who replaced them were more circumspect about administering and prescribing opioids (5).

For the rest of the twentieth century, opioid addiction epidemics resulted from transient increases in the incidence of nonmedical heroin use in urban areas. After World War II, these epidemics disproportionately affected inner-city minority populations, such as the large, heavily publicized increase in ghetto heroin use and addiction at the end of the 1960s (24, 37).

THE SHARP RISE IN PRESCRIPTION OPIOID CONSUMPTION

In 1986 a paper describing the treatment of 38 chronic pain patients concluded that OPRs could be prescribed safely on a long-term basis (61). Despite its low-quality evidence, the paper was widely cited to support expanded use of opioids for chronic non-cancer pain. Opioid use increased gradually in the 1980s. In 1996, the rate of opioid use began accelerating rapidly (38). This acceleration was fueled in large part by the introduction in 1995 of OxyContin, an extended release formulation of oxycodone manufactured by Purdue Pharma.

Between 1996 and 2002, Purdue Pharma funded more than 20,000 pain-related educational programs through direct sponsorship or financial grants and launched a multifaceted campaign to encourage long-term use of OPRs for chronic non-cancer pain (86). As part of this campaign, Purdue provided financial support to the American Pain Society, the American Academy of Pain Medicine, the Federation of State Medical Boards, the Joint Commission, pain patient groups, and other organizations (27). In turn, these groups all advocated for more aggressive identification and treatment of pain, especially use of OPRs.

For example, in 1995, the president of the American Pain Society introduced a campaign entitled "Pain is the Fifth Vital Sign" at the society's annual meeting. This campaign encouraged health care professionals to assess pain with the "same zeal" as they do with vital signs and urged more aggressive use of opioids for chronic non-cancer pain (9). Shortly thereafter, the Veterans' Affairs health system, as well as the Joint Commission, which accredits hospitals and other health care organizations, embraced the Pain is the Fifth Vital Sign campaign to increase the identification and treatment of pain, especially with OPRs. Similarly, the American Pain Society and the American Academy of Pain Medicine issued a consensus statement endorsing opioid use for chronic non-cancer pain (31). Although the statement cautioned against imprudent prescribing, this warning may have been overshadowed by assertions that the risk of addiction and tolerance was low, risk of opioid-induced respiratory depression was short-lived, and concerns about drug diversion and abuse should not constrain prescribing.

Prior to the introduction of OxyContin, many physicians were reluctant to prescribe OPRs on a long-term basis for common chronic conditions because of their concerns about addiction, tolerance, and physiological dependence (80). To overcome what they claimed to be "opiophobia," physician-spokespersons for opioid manufacturers published papers and gave lectures in which they claimed that the medical community had been confusing addiction with "physical dependence." They described addiction as rare and completely distinct from so-called "physical dependence," which was said to be "clinically unimportant" (60, p. 300). They cited studies with serious methodological flaws to highlight the claim that the risk of addiction was less than 1% (28, 45, 52, 59, 62).

In addition to minimizing risks of OPRs, the campaign advanced by opioid manufacturers and pain organizations exaggerated the benefits of long-term OPR use. In fact, high-quality,

long-term clinical trials demonstrating the safety and efficacy of OPRs for chronic non-cancer pain have never been conducted. Surveys of patients with chronic non-cancer pain receiving long-term OPRs suggest that most patients continued to experience significant chronic pain and dysfunction (25, 76). The CDC and some professional societies now warn clinicians to avoid prescribing OPRs for common chronic conditions (29).

Although increased opioid consumption over the past two decades has been driven largely by greater ambulatory use for chronic non-cancer pain (8), opioid use for acute pain among hospitalized patients has also increased sharply. A recent study found that physicians prescribed opioids in more than 50% of 1.14 million nonsurgical hospital admissions from 2009 to 2010, often in high doses (34). The Joint Commission's adoption of the Pain is the Fifth Vital Sign campaign and federally mandated patient satisfaction surveys asking patients to rate how often hospital staff did "everything they could to help you with your pain" are noteworthy, given the association with increased hospital use of OPRs.

REFRAMING THE OPIOID CRISIS AS AN EPIDEMIC OF ADDICTION

Policy makers and the media often characterize the opioid crisis as a problem of nonmedical OPR abuse by adolescents and young adults. However, several lines of evidence suggest that addiction occurring in both medical and nonmedical users, rather than abuse per se, is a key driver of opioid-related morbidity and mortality in medical and nonmedical OPR users.

Opioid Harms Are Not Limited to Nonmedical Users

Over the past decade, federal and state policy makers have attempted to reduce OPR abuse and OPR-related overdose deaths. Despite these efforts, morbidity and mortality associated with OPRs have continued to worsen in almost every US state (10). Thus far, these efforts have focused primarily on preserving access to OPRs for chronic pain patients while reducing nonmedical OPR use (89), defined as the use of a medication without a prescription, in a way other than as prescribed, or for the experience or feeling it causes. However, policy makers who focus solely on reducing nonmedical use are failing to appreciate the high opioid-related morbidity and mortality in pain patients receiving OPR prescriptions for medical purposes.

The incidence of nonmedical OPR use increased sharply in the late 1990s, peaking in 2002 with 2.7 million new nonmedical users. Since 2002, the incidence of nonmedical use has gradually declined to ~1.8 million in 2012 (64, 70) (**Figure 3**). Although the number of new nonmedical users has declined, overdose deaths, addiction treatment admissions, and other adverse public health outcomes associated with OPR use have increased dramatically since 2002.

A comparison of age groups of nonmedical OPR users to age groups suffering the highest rates of opioid-related morbidity and mortality suggests that strategies focused exclusively on reducing nonmedical OPR use are insufficient (**Figure 4**). Although past-month nonmedical use of OPRs is most common in teenagers and young adults between the ages of 15 and 24 (65), OPR overdose deaths occur most often in adults ages 45–54, and the age group that has experienced the greatest increase in overdose mortality over the past decade is 55–64 (15), an age group in which medical use of OPRs is common. Opioid overdoses appear to occur more frequently in medical OPR users than in young nonmedical users. For example, in a study of 254 unintentional opioid overdose decedents in Utah, 92% of the decedents had been receiving legitimate OPR prescriptions from health care providers for chronic pain (39).

Middle-aged women and the elderly are more likely than other groups to visit doctors with complaints of pain (4). The development of iatrogenic opioid addiction in these groups may explain why they have experienced the largest increase in hospital stays resulting from opioid user

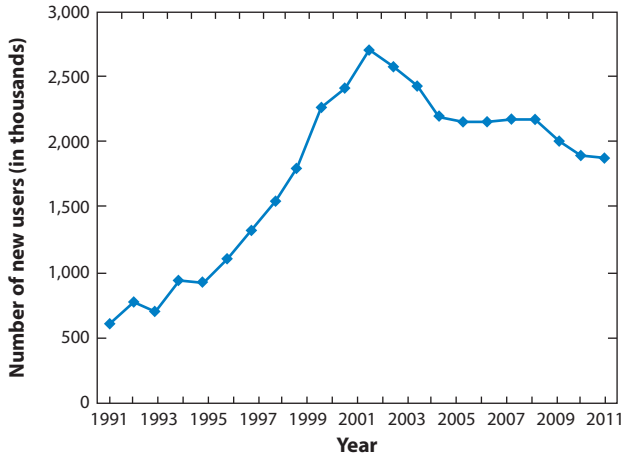

Figure 3

First-time nonmedical use of pain relievers. Source: 64, 70.

disorders since 1993 (56) (**Figure 5**). Over the past decade, white women ages 55–64 have also experienced the largest increase in accidental opioid overdose deaths (12, 15).

Opioid Addiction Is a Key Driver of Morbidity and Mortality

Accidental opioid overdose is a common cause of death in individuals suffering from opioid addiction (36). Although overdoses do occur in medical and nonmedical OPR users who are not

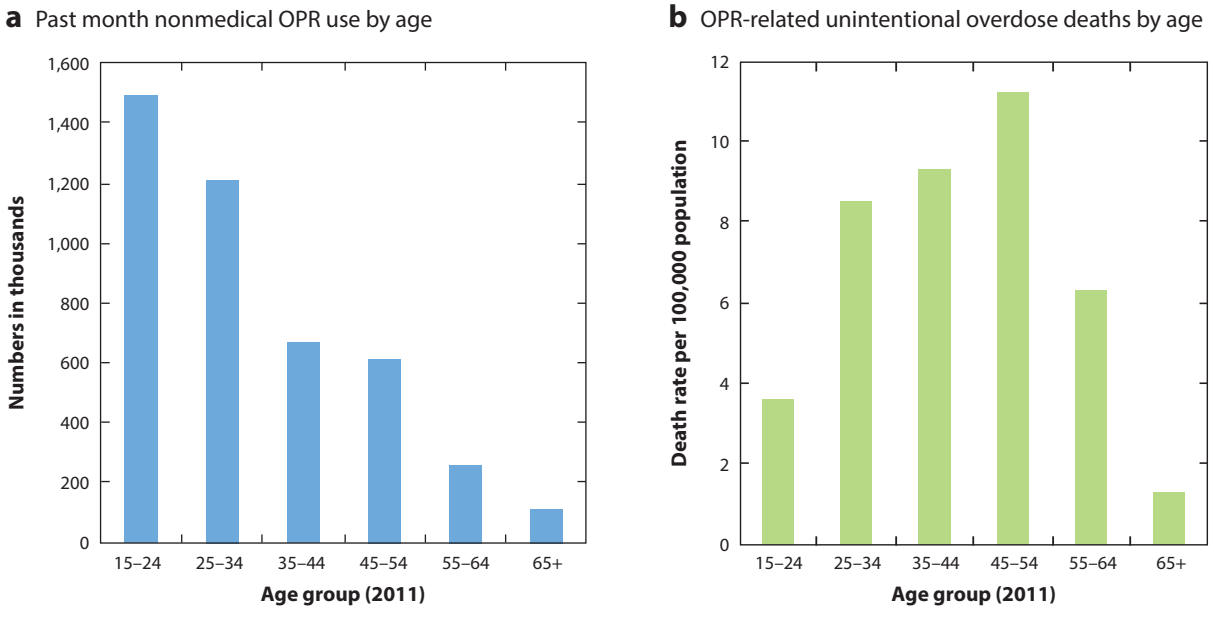

Figure 4

(*a*) Past month nonmedical OPR use by age versus (*b*) OPR-related unintentional overdose deaths by age. Abbreviation: OPR, opioid pain reliever. Sources: 58, 68.

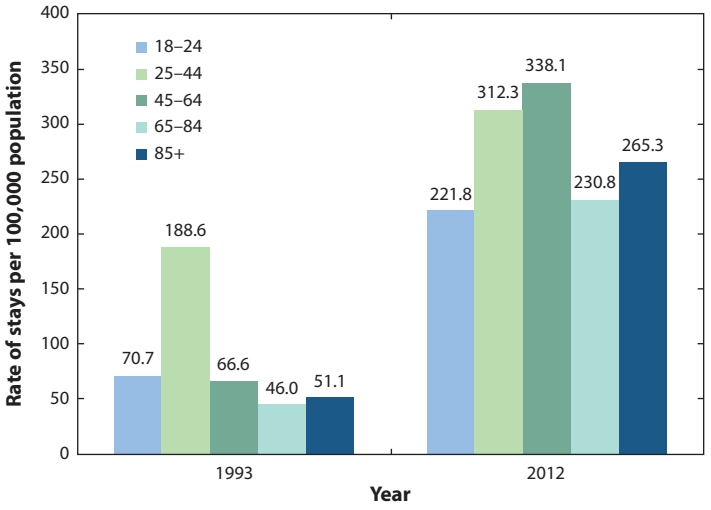

Figure 5

Rate of hospital inpatient stays related to OPR use by adult age group, 1993 and 2012. Source: 56.

opioid-addicted, consistent findings in samples of OPR overdose decedents show that deaths are most common in individuals likely to be suffering from opioid addiction. A study of 295 unintentional OPR overdose deaths in West Virginia found that four out of five decedents (80%) had a history of a substance use disorder (33). Another study found that among 254 opioid overdose decedents in Utah, about three-fourths (76%) had relatives or friends who were concerned about the decedent's misuse of opioids prescribed for pain (39).

The sharp increase in the prevalence of opioid addiction is a key driver of opioid-related morbidity and mortality. The misattribution of the opioid crisis to nonmedical use or abuse rather than to addiction has stymied efforts to address this crisis because it has led to a focus on policies to prevent such nonmedical use at the expense of greater resources committed to preventing and treating opioid addiction in both medical and nonmedical users.

PREVENTION STRATEGIES

This section organizes strategies for curbing the epidemic of opioid addiction into primary, secondary, and tertiary prevention. Although some specific interventions are discussed, we do not provide an exhaustive list. Rather, our purpose is to demonstrate that prevention strategies employed in epidemiologic responses to communicable and noncommunicable disease epidemics apply equally well when the disease in question is opioid addiction. Interventions should focus on preventing new cases of opioid addiction (primary prevention), identifying early cases of opioid addiction (secondary prevention), and ensuring access to effective addiction treatment (tertiary prevention).

Primary Prevention

The aim of primary prevention is to reduce the incidence of a disease or condition. Opioid addiction is typically chronic, life-long, difficult to treat, and associated with high rates of morbidity and mortality. Thus, bringing the opioid addiction epidemic under control requires effort to prevent new cases from developing.

Preventing addiction caused by medical exposure to OPRs. The incidence of iatrogenic opioid addiction in patients treated with long-term OPRs is unknown because adequately designed prospective studies have not been conducted. However, opioid use disorders appear to be highly prevalent in chronic pain patients treated with OPRs. A survey performed by Boscarino et al. of 705 chronic pain patients treated in specialty and primary care outpatient centers found that 26% met the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) IV criteria for opioid dependence, and 35% met DSM V criteria for an opioid use disorder (6, 7). A systematic review of studies utilizing opioids for low back pain found that aberrant drug abuse–related behaviors suggestive of addiction occurred in up to 24% of patients on long-term OPRs (50). Many patients on long-term OPRs worry about dependence and addiction and express a desire to taper or cease opioid therapy (76).

To reduce the incidence of iatrogenic opioid addiction, health care professionals must prescribe opioids more cautiously for both acute and chronic pain. Unfortunately, the campaign to encourage OPR prescribing has left many health care providers with a poor appreciation of opioid risks, especially the risk of addiction, and an overestimation of opioid benefits. Despite these risks and the lack of evidence supporting long-term efficacy, OPR prescribing for chronic non-cancer pain increased over the past decade while use of nonopioid analgesics decreased (20). This pattern highlights the need for prescriber education that explicitly corrects misperceptions about OPR safety and efficacy. If clinicians treating pain more often substituted nonopioid analgesics and nonpharmaceutical approaches for OPRs, evidence suggests the incidence of opioid addiction would decline and outcomes for patients with chronic non-cancer pain would improve.

Many prescribers are unaware that evidence of long-term effectiveness for OPRs is lacking and that risks, in addition to addiction, include respiratory depression leading to unintentional overdose death; serious fractures from falls (71, 77); hypogonadism and other endocrine effects that can cause a spectrum of adverse effects (88); increased pain sensitivity (2); chronic constipation and serious fecal impaction (81); and chronic dry mouth, which can lead to tooth decay (79). Providing prescribers with accurate information about opioid risks and benefits could result in more informed risk/benefit appraisals. Indeed, one of the lessons learned from the nineteenth-century opioid addiction epidemic was that physicians were educable. By the early 1900s, aggressive opioid prescribing had become the hallmark of older, less-competent physicians (5).

Several states, including Iowa, Kentucky, Massachusetts, Ohio, Tennessee, and Utah, have passed mandatory prescriber education legislation (89). In addition, the US Food and Drug Administration (FDA) is requiring manufacturers of extended release and long-acting OPRs to sponsor educational programs for prescribers. Unfortunately, some of these educational programs, including those required by the FDA, imply that OPRs are safe and effective for chronic non-cancer pain instead of offering prescribers accurate information about OPR risks and benefits (84). It remains unclear whether or not educational programs such as these will reduce OPR prescribing for common conditions where risks of use are likely to outweigh benefits.

Some opioid manufacturers have reformulated OPRs to make them more difficult to misuse through an intranasal or injection route. These so-called abuse-deterrent formulations (ADFs) may offer safety advantages over easily snorted and injected OPRs, but they do not render them less addictive. Opioid addiction, in both medical and nonmedical OPR users, most frequently develops through oral use (85). Some opioid-addicted individuals may transition to intranasal or injection use, but most continue to use OPRs orally (47). Thus, ADFs should not be considered a primary prevention strategy for opioid addiction.

In 2013, the New York City Department of Health and Mental Hygiene released emergency room guidelines on OPR prescribing (55). Recommendations included in the guidelines call for substituting nonopioid analgesics when possible, avoiding use of extended-release OPRs, and

limiting the supply to three days. Reducing patient exposure to OPRs and reducing the supply of excess OPRs in the homes of discharged patients may be effective strategies for preventing opioid addiction that can occur from both medical and nonmedical OPR use.

Preventing addiction caused by nonmedical exposure to OPRs. Individuals who use OPRs nonmedically are at risk for developing opioid addiction. Thus, efforts to reduce nonmedical use are an important primary prevention strategy. Adolescents and young adults who experiment with nonmedical use are most likely to obtain OPRs for free from friends or family members who had received a legitimate prescription (70). This information suggests that more cautious prescribing is required to prevent nonmedical use of excess OPRs. Unused OPRs in medicine chests should be immediately discarded or returned to a pharmacy, which became permissible in October 2014 after the Drug Enforcement Administration made a federal regulatory change (82).

Although OPRs have an abuse liability similar to that of heroin (17), they are commonly perceived as less risky. Seventy-three percent of eighth graders surveyed in 2013 perceived occasional use of heroin without a needle as high risk, but only 26% perceived occasional use of Vicodin as high risk (41). Eighth graders also perceived occasional Vicodin use as less risky than occasional marijuana use, less risky than smoking 1–5 cigarettes per day, and less risky than moderate alcohol use.

Individuals who perceive the risk of nonmedical OPR use to be low may be more likely to misuse OPRs. A 2004 survey found that college students who perceive a low level of risk from OPRs were 9.6 times more likely to use OPRs nonmedically, as compared with those who perceive these medications as harmful (3). Although the ability for causal inference from this type of cross-sectional survey is limited, this finding suggests that social marketing campaigns designed to increase perceived harmfulness of OPRs may be an effective prevention strategy.

Secondary Prevention

The aim of secondary prevention is to screen for a health condition after its onset but before it causes serious complications. Efforts to identify and treat opioid-addicted individuals early in the course of the disease are likely to reduce the risk of overdose, psychosocial deterioration, transition to injection opioid use, and medical complications.

Physicians are frequently the source of OPRs for opioid-addicted medical and nonmedical users (43). Contacts with medical professionals present valuable opportunities for early identification of opioid addiction. However, detection of opioid addiction in OPR users can be very difficult. Opioid-addicted chronic pain patients may demonstrate aberrant drug-related behaviors, such as presenting for early refills. However, some opioid-addicted pain patients, especially those prescribed high doses, may not demonstrate drug-seeking behavior. Opioid-addicted individuals receiving OPR prescriptions are often reluctant to disclose their concerns about addiction with prescribers because they fear being judged, being cut off from a legitimate supply, or being labeled as malingerers for feigning pain.

The difficulty of diagnosing opioid addiction in individuals motivated to conceal their condition suggests that prescribers should seek collateral information before prescribing OPRs. Urine toxicology can be used to verify a patient's self-reported drug ingestion history (53). However, urine toxicology of patients on long-term OPRs is not a reliable strategy for identifying opioid addiction. Urine toxicology cannot determine if a patient is taking extra doses or if a patient is using OPRs by an intranasal or injection route.

Opioid-addicted individuals may receive OPR prescriptions from multiple providers, a practice referred to as "doctor shopping." Doctor shoppers can be identified through use of state

prescription drug monitoring programs (PDMPs). Some state PDMPs send unsolicited reports to the medical providers of doctor shoppers. Research suggests that unsolicited reports increase prescribers' ability to detect opioid addiction, sometimes prompting actions such as coordinating care with other providers and modifying their own prescribing practices, as well as screening and referring for addiction treatment (78).

Prescribers in most states can consult their state PDMP before prescribing OPRs. PDMPs may be especially useful in emergency rooms and other settings where opioid-addicted individuals feign pain to obtain OPRs. Too often, however, patients identified as doctor shoppers are simply turned away, without hospital staff attempting to link these patients to addiction treatment services. Efforts must be made to help these clinicians understand that drug-seeking patients are suffering from the chronic, life-threatening disease of opioid addiction.

One challenge to PDMP effectiveness has been the low rate of provider use of these data (48). To increase prescriber utilization, Kentucky, Tennessee, and New York passed legislation mandating that prescribers check the PDMP before prescribing controlled substances. Data from these states indicate that PDMP utilization increased rapidly subsequent to the mandate, which correlated with declines in opioid prescribing (KY, TN, NY) and a sharp drop in visits to multiple providers (TN, NY) (35).

Tertiary Prevention

Tertiary prevention strategies involve both therapeutic and rehabilitative measures once a disease is firmly established. The goal of tertiary prevention of opioid addiction is to prevent overdose deaths, medical complications, psychosocial deterioration, transition to injection drug use, and injection-related infectious diseases. Doing so is accomplished mainly by ensuring that opioid-addicted individuals can access effective and affordable opioid addiction treatment.

Opioid addiction treatment. The need for opioid addiction treatment is great and largely unmet. According to the NSDUH, an estimated 2.1 million Americans are addicted to OPRs, and 467,000 are addicted to heroin (70). Unfortunately, these estimates exclude many opioid-addicted pain patients because NSDUH participants are told by surveyors that "we are only interested in your use of prescription pain relievers that were not prescribed for you or that you used only for the experience or feeling they caused" (67, p. 124).

In 2005, there were an estimated 10 million chronic pain patients receiving daily, long-term treatment with OPRs (8). The continuing increase in opioid consumption from 2005 to 2011 (42) suggests that the number may now exceed 10 million. Applying the prevalence estimates of DSM IV opioid dependence found by Boscarino et al. (6) in pain patients taking long-term opioids would indicate that an additional 2.5 million chronic pain patients may be opioid-addicted. Thus, the total number of Americans suffering from opioid addiction may exceed 5 million.

Treatment of opioid addiction includes pharmacotherapies and psychosocial approaches, including residential treatment, mutual-help programs (e.g., Narcotics Anonymous), and 12-Step treatment programs. These modalities may be used as stand-alone interventions or in combination with pharmacotherapy. Psychosocial opioid addiction treatment approaches show value and are an important treatment option (63). However, research with greater specificity and consistency is needed to better evaluate outcomes.

Pharmacotherapies for opioid addiction include agonist maintenance with methadone and partial-agonist maintenance with buprenorphine and antagonist treatment with naltrexone, which is available in a monthly injection. Methadone and buprenorphine work by controlling cravings. Naltrexone works by preventing opioid-addicted individuals from feeling the effects of opioids.

Naltrexone may be helpful in highly motivated and carefully selected patients. However, patients treated with naltrexone may be at increased risk of overdose death should relapse occur (23).

Multiple well-designed randomized controlled trials provide strong evidence that buprenorphine maintenance and methadone maintenance are safe and effective treatments for opioid addiction (30, 40, 46, 49, 74, 75). Both buprenorphine and methadone treatment are associated with reduced overdose risk and improved maternal and fetal outcomes in pregnancy (19, 44, 51, 72). Despite strong evidence supporting the use of buprenorphine and methadone, fewer than 1 million Americans are receiving these treatments (87).

Methadone poses a substantially greater risk of respiratory depression than does buprenorphine and can be obtained only from licensed opioid treatment programs (OTPs). The lack of OTPs in many communities presents a major challenge to expanding access to methadone. In contrast, buprenorphine, a partial opioid agonist, has a better safety profile than does methadone and can be prescribed in an office-based setting (26). Barriers to accessing buprenorphine include federal limits on the number of patients a physician may treat, ineligibility of nurse practitioners to prescribe it, and inadequate integration of buprenorphine into primary care treatment. Access to buprenorphine treatment could be expanded if the federal government eased or remove regulatory barriers.

Harm-reduction approaches. Tertiary prevention strategies also include harm-reduction approaches to improving health outcomes and reducing overdose deaths. In the subset of opioid-addicted individuals who are heroin injection drug users, evidence suggests that access to syringe exchange programs can prevent HIV infection (22). These efforts have been less effective at preventing hepatitis C infection, which is increasing rapidly in young, white IDUs (32).

Expanding access to naloxone, an opioid overdose antidote, can prevent overdose deaths by reversing life-threatening respiratory depression. In the 1990s, syringe exchange programs began distributing naloxone to injection drug users for the purpose of rescuing peers. Evidence shows that clients of syringe exchange programs demonstrated the ability to successfully reverse overdoses when they had been provided with naloxone and training (73). In addition, providing family members of opioid-addicted individuals and nonparamedic first responders with naloxone may be an effective strategy for rescuing overdose victims (21, 90). At present, there are more than 188 community-based naloxone distribution programs in 15 states and the District of Columbia (11).

CONCLUSION

The increased prevalence of opioid addiction, caused by overprescribing of OPRs, has led to a parallel increase in opioid overdose deaths. Efforts to address this crisis that focus exclusively on reducing nonmedical OPR use have been ineffective. Middle-aged and elderly individuals commonly exposed to OPRs for pain treatment have experienced the largest increase in rates of opioid-related morbidity and mortality. Recognition that opioid addiction in both medical and nonmedical users is a key driver of opioid-related morbidity and mortality will result in a more effective response to this public health crisis. Just as public health authorities would approach other disease outbreaks, efforts must be made to reduce the incidence of opioid addiction, identify cases early, and ensure access to effective treatment.

Preventing opioid addiction requires strategies that foster more cautious and selective OPR prescribing. However, if prescribing is reduced without also ensuring access to addiction treatment, the opioid overdose death rate may remain at a historically high level and the use of heroin may continue to increase. Coordinated efforts from federal agencies, state agencies, health care insurers, and health care providers are required to address the needs of millions of Americans now struggling with this chronic, life-threatening disease.

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REVIEW | Annals of Internal Medicine

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

Teryl K. Nuckols, MD, MSHS; Laura Anderson, MPH; Ioana Popescu, MD, MPH; Allison L. Diamant, MD, MSHS; Brian Doyle, MD; Paul Di Capua, MD; and Roger Chou, MD

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.

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For author affiliations, see end of text.

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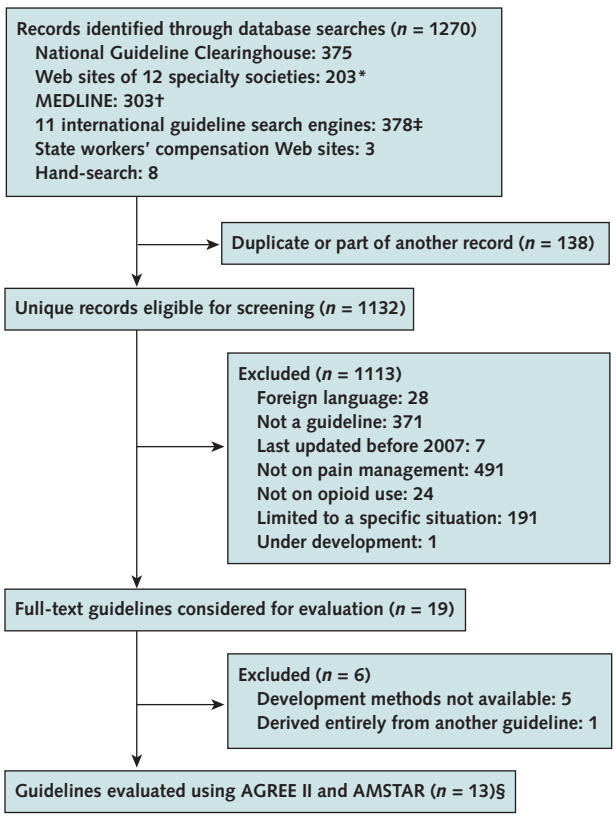
Appendix Figure. **Summary of evidence search and selection.**



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.