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AOA Critical Issues

Leading the Way to Solutions to the Opioid Epidemic

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Background: In the past 2 decades, overdoses and deaths from prescription opioids have reached epidemic proportions in the United States. The widespread use of opioids complicates management of the orthopaedic surgery patient in the acute and chronic settings. Orthopaedic surgeons are some of the top prescribers of opioids in the complex setting of chronic use, abuse, and diversion.

Methods: The literature regarding the basic science of pharmacologic options for pain management (e.g., opioids and nonsteroidal anti-inflammatory drugs), the impact of strategies on bone and soft-tissue healing, and pain relief are summarized as they relate to the management of orthopaedic injuries and conditions. Additionally, a section on designing solutions to address the current opioid crisis is presented.

Results: The mechanism of action of different classes of analgesic medications is discussed, as well as the basic scientific evidence regarding the impact of narcotic and nonnarcotic analgesic medications on bone-healing and on other organ systems. Differences between pain and nociception, various treatment strategies, and clinical comparisons of the effectiveness of various analgesics compared with opioids are summarized. Finally, options for addressing the opioid crisis, including the description of a large system-wide intervention to impact prescriber behavior at the point of care using health-information solutions, are presented.

Conclusions: Orthopaedic leaders, armed with information and strategies, can help lead the way to solutions to the opioid epidemic in their respective communities, institutions, and subspecialty societies. Through leadership and education, orthopaedic surgeons can help shape the solution for this critical public health issue.

Over the past 2 decades, the United States has entered an epidemic of abuse, misuse, and diversion of prescription opioids[1]. The U.S. consumes 80% of the world's prescription opioids, despite having <5% of the world's population[2]. Unintentional drug overdoses with prescription medication have reached alarming numbers[3,4]. In 2001, The Joint Commission introduced mandatory pain assessment standards for all patients and cited the American Pain Society and Department of

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Veterans Affairs "pain is the fifth vital sign" as an example of a strategy for some clinical settings[5]. This helped to increase the awareness of physicians and health-care providers regarding patient comfort; however, a sharp rise in prescription overdose deaths began during this same time frame. In 2008, >36,000 people died from drug overdoses, and these numbers have continued to rise, with >38,000 deaths in 2010[4,6]. This represents a threefold rise in the United States in <25 years[4]. Poisonings, which are 90% drug related, are now the leading cause of death after injuries, including motor-vehicle collisions, in the U.S.[7].

Furthermore, misuse of prescription pain medicine accounts for nearly half a million emergency department visits a year[8]. More than 75% of these people are using drugs that have been prescribed to another person (diversion)[9].

The field of orthopaedic surgery has a few critical roles relative to the opioid crisis. A recent study demonstrated that while we make up only 2.5% of U.S. physicians, we prescribe almost 8% of the narcotic analgesics. This puts orthopaedic surgeons at number 4 on the list of top prescribers by specialty[10]. Prescription rates have risen throughout the country in the past 15 to 20 years, with several states demonstrating numbers of prescriptions in a year similar to the entire population in the state[11].

As a result, it has been increasingly common for patients to use opioids chronically from a variety of sources prior to undergoing orthopaedic surgery. Regrettably, these preoperative opioids have been associated with increased length of hospital stay, morbidity, worse outcome, and extended postoperative opioid use[12-17], which in turn impacts surgeons and hospitals in this era of quality measures and patient-reported outcomes.

Given the role of orthopaedic surgeons in prescribing opioids and the impact of opioids on our patients and treatment outcomes, this is a public health crisis that needs leadership from our community. While this may seem like an overwhelming task, high death rates from motor-vehicle collisions a few decades ago were greatly reduced by the collaboration of government agencies, health-care organizations, automotive manufacturers, and law enforcement[18]. Steps for orthopaedic surgeons toward leading the way to solutions to the opioid epidemic include the following: (1) understanding the evidence behind the use of opioid and nonopioid analgesics and the risk of our opioid-centric pain strategies; (2) taking a comprehensive and attentive approach to pain relief that accounts for variation in pain intensity for a given nociception, which can be influenced by stress[19], distress, and coping strategies[20,21], as well as self-efficacy[22-24] (confidence in oneself and/or pain management ability), resilience (ability to recover from setbacks and/or adapt in stressful situations)[25-28], or high catastrophic thinking[29-31]; and (3) working collaboratively with patients to develop strategies for better pain relief and safer prescribing strategies for practices, hospitals, and hospital systems.

The Evidence

The term "opioid" has come to be a catchall term representing opiates (e.g., morphine derived directly from opium), semi-synthetic opiates (e.g., oxycodone derived from extracts of the opium poppy), and synthetic opiates (e.g., fentanyl). The source of the active drug in opioids, except for the purely synthetic compounds, remains the extruded latex from the opium poppy seed pod[32]. This opium residue can be converted to morphine, heroin, or alkaloid compounds, which can eventually become oxycodone or hydrocodone[33].

Opioid monotherapy rose to prominence in the past 2 decades because of a variety of factors, including aggressive marketing by pharmaceutical companies, organizational mandates of pain assessments, and a simultaneous growing fear among orthopaedic surgeons of the bone-healing impact of nonsteroidal anti-inflammatory drugs (NSAIDs).

While opioids have long been used to treat acute pain following traumatic injury and during the postoperative period, the expansion of the use of these opioid analgesics to noncancer pain outside of the acute or immediate postoperative setting started to become more commonplace in the 1990s, based on the conclusions published by Portenoy and Foley in 1986[34]. Their publication claimed the safety and efficacy of opioids for chronic noncancer pain, despite small patient numbers (38) culled from 2 different studies with moderate results and several complications. At that time, extended-release oxycodone (OxyContin) entered the marketplace with claims of increased efficacy and safety. Subsequently, the manufacturer admitted to false marketing on the safety of OxyContin[35], and studies have not demonstrated the increased efficacy of extended release over immediate release[36-41]. Pain advocacy groups and pain specialists, many of whom have substantial financial relationships with pharmaceutical companies, successfully lobbied organizations such as the Federation of State Medical Boards, the Veterans Health Administration, and The Joint Commission to put pain at the center of all patient assessments. Physicians faced increased pressure to prescribe more opioids[42]. This opened the door for aggressive marketing by pharmaceutical companies to expand the use of opioids to noncancer pain; the marketing included educational materials supplied by The Joint Commission, which were sponsored by Purdue Pharma[43].

With respect to the efficacy of opioids for noncancer pain, there are mixed results in the literature. Meta-analyses demonstrate a moderate effect size of opioids compared with placebos for pain relief (-0.60[44], -0.57[45]), but similar efficacy compared with NSAIDs and tricyclic anti-depressants (-0.05[45]). Of concern, most studies were sponsored by the pharmaceutical manufacturers, and the higher-quality studies ended at 6 to 16 weeks; therefore, longer-term efficacy was not tested[45].

With respect to safety, "a 1% risk of addiction" is commonly cited[46-52]. According to a published 1-paragraph letter to the editor in *The New England Journal of Medicine,* this percentage was based on limited exposure with inpatients (without publication of study methods)[53]. Subsequent studies have demonstrated that the risk of addiction to prescription opioids is 3% to 45% when they are used on a long-term basis. Furthermore, if patients take prescription opioids beyond 12 weeks,

50% will still be taking them at 5 years[54]. The 90-day conversion to long-term use and increased risk has been corroborated in other studies[55-58].

Bone and Soft-Tissue Healing

Some basic science studies and some sparse clinical studies created fear among orthopaedic surgeons regarding the suppression of bone formation with the use of NSAIDs. Many of these animal models were spinal fusion models, and fracture-healing models yielded mixed results at best[59].

Two clinical studies rise above the rest for raising alarm over the use of NSAIDs in fracture-healing. Giannoudis et al. used a retrospective case control model to examine nonunion in nailed femoral shaft fractures[60]. The rather shocking odds ratio for nonunion with the use of NSAIDs was reported as 10.7, but the sample was underpowered, and NSAID use was severely underrepresented in the control group. Sagi et al. showed a high rate of nonunion of the acetabular posterior wall in the group of patients with the longest duration of indomethacin use in their randomized trial of heterotopic ossification prophylaxis; however, there were only 13 patients in this group[61]. While isolated clinical investigations such as these have been cited as evidence to withhold NSAIDs during fracture treatment, critical examination of the clinical literature does not support this conclusion. Two recent comprehensive clinical meta-analyses have demonstrated that there is no high-quality literature support for NSAID inhibition of fracture-healing[62,63]. The influence of NSAIDs on fracture-healing is important to understand because these medications may serve as a safer and equally effective alternative to opiates for pain control during fracture treatment.

There has been very little scientific investigation into the clinical effects of opiates on fracture-healing. In 2005, Bhattacharyya et al. published a database review to examine the effect of NSAIDs on humeral fracture-healing, but they found a potentially confounding effect with the association of prolonged use of opiates after fracture and humeral nonunion[64]. A separate examination by Brinker et al. into the metabolic causes of nonunion listed hypogonadism (low testosterone) as a potential cause of nonunion[65].

Based on the unknown role of opiates on fracture-healing, recent investigations have tried to determine a potential effect of opiate analgesics on fracture-healing. Chrastil et al. used a rat femur fracture model to examine opiate influence, and found that subjects treated with opiate analgesia formed callus in greater volume, but the callus was more disorganized and mechanically weaker than in the control animals[66,67]. OPIAD (opioid-induced androgen deficiency) syndrome describes the naturally occurring reduction in serum testosterone seen clinically with both acute and chronic opiate administration. Chrastil and colleagues attempted to determine if supplemental testosterone might be used to mitigate the effects of opiates on callus formation and strength, but their 2014 publication found that this was not effective[67]. This study casts doubt on the theory that the effect of opiates on bone-healing is solely mediated by hypogonadism because the opiate-treated animals demonstrated a drop in serum testosterone, but still had impaired callus formation, despite administration of supplemental exogenous testosterone. Overall, any conclusions on the role of opiates in bone-healing are very preliminary, but the field certainly merits additional bench and clinical investigation given its potentially profound impact on clinical practice.

Contradictory basic science data also exist with regard to the impact of NSAIDs on tendon and ligament-healing. Some studies warn against early use and against avoiding late use, while others recommend the opposite[68,69]. Some of the animal studies find detrimental effects of NSAIDs on tendon-to-bone healing[70,71], while others suggest the contrary[72]. Some clinical trials suggest that the use of NSAIDs is safe, but leave room for additional study[73,74].

Pain Relief

Nociception is the physiology of actual or potential tissue damage. Pain is the cognitive, emotional, and behavioral response to nociception. Pain intensity varies substantially for a given nociception from person to person. This variation may be accounted for in part by stress (e.g., illness in the family, job insecurity, financial concerns), distress (e.g., symptoms of depression and anxiety), and less effective coping strategies (e.g., catastrophic thinking, kinesiophobia, and low self-efficacy)[75]. In other words, pain intensity and psychosocial factors are linked. It can be argued that the opioid-centric pain management strategies that contributed to the current epidemic of opioid misuse and overdose deaths diverted attention from these aspects of normal illness behavior in humans, thereby contributing to ineffective pain relief for patients with musculoskeletal

TABLE I Example Discussion Scripts to Discuss Pain Management

Script	Examples
Manages expectations and reminds the patient that surgery will hurt	"What did you do for pain after your last surgery?" "We'll give you a few opioid pills for the first 1 to 2 nights, but during the day, you should be on acetaminophen or ibuprofen (or both)."
Alternative strategies to managing pain	"Use ice and elevation." "Try to get back to your normal routine as quickly as possible." "Find ways to distract yourself with friends or family."

TABLE II Opioid-Sparing Strategies*

Practices and departments should establish policies and abide by them:
Evidence supports that policies reduce the use of opioids and the number of unused pills available for diversion
Standardize framework for discussion with patients about opiates ("I wish I could give you more, but it's against the policy and I'll get in trouble. Let's talk about other ways to get you comfortable")
Promote alternative pain-management strategies (e.g., ice, elevation, relaxation, guided imagery, etc.)
Recommend use of ibuprofen or acetaminophen rather than relying on opioids
Check the PDMP consistently
Coordinate pain relief with the patient's primary care doctor and/or other specialists
Only 1 doctor should provide opioids at a time
Discuss strategies for postsurgical pain management for patients with a history of substance abuse

*PDMP = Prescription Drug Monitoring Program.

disease and injury. To help our patients get comfortable, we need to develop, support, and champion comprehensive approaches to pain relief.

Patients in the Netherlands leave the hospital after operative fixation of an ankle fracture with acetaminophen or tramadol; they are equally or more satisfied with their pain relief than patients taking oxycodone in the U.S.[76]. In the United States, patients recovering from fracture or other orthopaedic surgeries have more pain if they take more opioids, independent of the degree of surgery, the number of fractures, or other surrogates for nociception[77,78]. The best pain reliever is self-efficacy in response to nociception (e.g., "This hurts, but I know it will be OK," or "It's going to be difficult for a while, but I'll get back on track")[77,78]. The factors most strongly associated with greater pain intensity for a given nociception are greater symptoms of depression and greater catastrophic thinking—the primordial human adaptation to "prepare for the worst" (e.g., "Will the pain ever go?" "It feels like something's wrong," or "I'll never be myself again")[77,78].

Distress is alleviated by interventions that optimize the functioning of the human mind[75]. Some treatments are based on cognitive behavioral therapy[79]. More effective coping strategies can be taught, coached, and practiced. Resilience, the ability to recover and adapt in stressful situations, has been shown to mediate the relationship between pain and functional ability. While those with higher levels of resilience have lower levels of pain catastrophizing and are better able to set goals for recovery, resilience can be cultivated and enhanced through cognitive behavioral interventions[25,26,28]. However, psychological treatments are undervalued and underdeveloped in clinical settings. The primary barriers to the comprehensive treatment of human illness are the tendency of the human mind to create a false mind-body dichotomy, combined with the stigma associated with psychology (i.e., the tendency of a person experiencing substantial symptoms of depression to feel abnormal, broken, and ashamed). It is more socially acceptable to say "I hurt" than it is to say "I'm down" or "I can't shake the feeling that…"[75].

Orthopaedic surgeons may not be experts in psychology, but we encounter the psychosocial aspects of human illness behavior every day[80-82]. We can appreciate the verbal and nonverbal signs of stress, distress, and less-effective coping strategies[81]. We can practice effective, empathic communication strategies that help us gain people's trust[83]. Discussion scripts

TABLE III Strategies for Perioperative Pain Management*

Physical Strategies	Cognitive/Mental Strategies	Pharmaceutical Strategies
• Cryotherapy[100-102]	• Cognitive-behavioral therapy[113-115]	• Field or nerve block[122-127]
• TENS[103]	• Meditation[116]	• NSAIDs[62,88,89]
• Massage[104,105]	• Guided imagery[117-119]	• Gabapentin[128]
• Healing Touch[106]	• Mindfulness-based stress reduction[120]	
• Reiki[107]	• Music therapy[121]	
• Acupuncture[108-110]		
• Aromatherapy[111,112]		

*TENS = transcutaneous electrical nerve stimulation and NSAIDs = nonsteroidal anti-inflammatory drugs.

TABLE IV Risk Factors Associated with Misuse, Abuse, or Diversion of Prescription Drugs*

Demographic Characteristics	Medical Conditions	Prescription Details	High-Risk Behaviors
• Race (Caucasian, non-Hispanic, American Indian/Alaskan native) • High school education or less • Age (younger to middle aged) • Not married • Financial problems • Unemployed • Male • Income extremes • Rural residence • LGBT • Public insurance • Low social class • Family history of substance abuse • Preadolescent sexual abuse	• Past suicide attempt • Lifetime heroin use • Pain • Tobacco use • Alcohol use • Current illicit drug use (including marijuana, cocaine, heroin, methamphetamine, hallucinogens) • Physical disability • Mental health problems • Substance abuse disorder • Hepatitis A, B, or C • Past hospitalization • Opioid dependence • Liver disease • Congestive heart failure • Cerebrovascular disease • Chronic pulmonary disease • Diabetes • Hypertension • Cancer • Cardiovascular disease • Obesity • Medical comorbidities • Past care at psychiatric hospital • ADHD	• Multiple prescribers • Multiple pharmacies • High community prescribing rates • Treatment with high-daily-dose opioids and short-acting opioids • Multiple prescriptions • Overlapping prescriptions • High maximum • of morphine-equivalent dose prescribed daily • Preexisting opioid use • Coprescribing of opioids and benzodiazepines	• Multiple prescribers • Multiple pharmacies • Multiple ED visits • Request for refill • Lost or stolen medication • Request for parenteral medication • Reported allergies to nonnarcotic medications • Requesting medication by name • Weekend visit • Use of alias • Abnormal urine/blood screen • Resist therapy changes/alternative therapy • Canceled clinic visits

*LGBT = lesbian, gay, bisexual, and transgender, ADHD = attention deficit hyperactivity disorder, and ED = emergency department.

can be developed and practiced for the most common and tricky office or inpatient encounters[84] (Table I). Most orthopaedic surgery is discretionary, which allows for plenty of time to screen patients for life stressors, symptoms of depression, less-effective coping strategies, and risk for opioid misuse, and to subsequently address any identified issues.

Orthopaedic surgeons are trained to treat the transient acute pain of injury and surgery. The Centers for Disease

TABLE V Risk Characteristics Programmed in EMR Alert System*

Early refill of current prescription with >50% remaining expected[70]
2+ visits to ED or Urgent Care with onsite treatment with opioids (not including visits leading to admission) within the previous 30 days[71-74]
3+ prescriptions for opioids or benzodiazepines within the previous 30 days[70,71,75-77]
Previous presentation for opiate or benzodiazepine overdose in the EMR[78]
Positive screen for blood alcohol, cocaine, or marijuana in the EMR[71,73,79-83]

*EMR = electronic medical record and ED = emergency department.

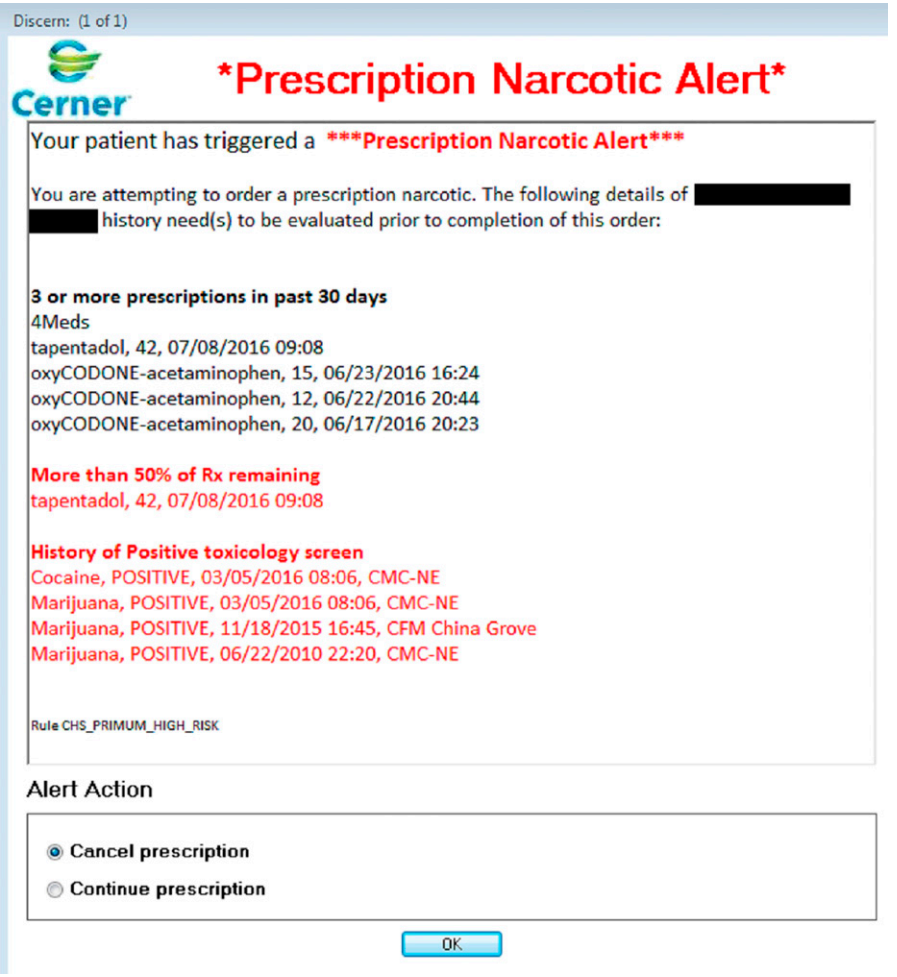

Fig. 1
Example of a prescription narcotic alert in an EMR.

Control and Prevention (CDC) guidelines for the treatment of chronic pain, released in March 2016, provide guidance for physicians. They recommend utilizing immediate-release opioids instead of extended-release opioids. The guidelines also provide a list of recommendations for the structure of treatment for chronic pain, including initiation of pain agreements, regular urine screening for drugs, and periodic reassessment of the treatment plan. This type of long-term management may be better suited to other medical specialties. Given the limited evidence of efficacy for persistent pain[85,86], opioid-sparing strategies from the onset of treatment for musculoskeletal injury or conditions might prevent long-term use. A list of opioid-sparing strategies is provided in Table II.

More and more, perioperative protocols[87-91] and evidence-based guidelines[92-94] are emerging in the literature. Utilization of NSAIDs, selective serotonin reuptake inhibitors (SSRIs), gabapentin, and injections for pain management in the perioperative and recovery periods is gaining attention. Multimodal perioperative pain management strategies for fracture care, as well as care related to joints, spine, sports, and other orthopaedic subspecialties, should include more than just pharmaceutical tactics. We should consider physical and cognitive/mental tactics as well (Table III).

Designing Solutions

Given the complex nature of the problem, designing solutions will require a multidisciplinary approach, including the collaboration of seemingly nontraditional partners for medical intervention. Physicians and other health-care providers from across multiple medical and surgical specialties (e.g., orthopaedic surgery, emergency medicine, internal medicine, family medicine, general surgery, oral medicine, etc.), public health researchers, epidemiologists, and pharmacists, as well as hospital administrators, policy analysts, and information-services personnel, need to collaborate.

First and foremost is the need for information at the point of care to help guide decision-making. A state-level strategy currently employed across 49 of the 50 U.S. states is the Prescription Drug Monitoring Program (PDMP). Oversight, monitoring, and access to PDMPs vary widely across the U.S., but all systems are designed as searchable, electronic databases that contain comprehensive information about

TABLE VI Recent National Progress Toward Safer Opioid Prescribing*

Surgeon General's letter to all U.S. physicians citing the opioid crisis, August 2016 (www.turnthetiderx.org)
The Centers for Medicare & Medicaid propose removal of pain-management dimension questions from the Hospital Value-Based Purchasing Program beginning in 2018 (https://www.cms.gov/Newsroom/MediaReleaseDatabase/Fact-sheets/2016-Fact-sheets-items/2016-07-06.html)
NEJM Special Report from FDA leadership: Califf RM, Woodcock J, Ostroff S. A proactive response to prescription opioid abuse (N Engl J Med 2016;374:1480-1485)
The Joint Commission releases a statement on pain management, clarifying 5 common misconceptions (April 18, 2016: https://www.jointcommission.org/joint_commission_statement_on_pain_management/)

*NEJM = New England Journal of Medicine and FDA = U.S. Food and Drug Administration.

controlled-substance prescriptions. While PDMPs represent a substantial source of information that is necessary for prescribers to make informed decisions about pain management for patients, there are several barriers and disadvantages to utilizing these programs. First, registration and access to the databases can be a barrier for many prescribers. Many states are working to streamline the registration process to make it easier for prescribers to obtain login accounts. Second, the prescriber must actively seek the information from the databases. Although some states have begun to require query of the PDMP prior to prescribing an opioid, this will be difficult to enforce. Finally, the number of prescriptions an individual currently has or has had within a certain amount of time is but 1 piece of the overall picture of a patient's risk of misuse, abuse, or diversion. Expanding efforts to primary, or even secondary, prevention is needed.

Currently, clinical-decision support systems, including alert systems, programmed into the electronic medical record (EMR) are designed to make the prescriber aware of critical information[95-97]. Multiple attempts to utilize the EMR and institute computerized physician-order entry have proven successful (e.g., allergy alerts, drug interactions, and contraindications). A persistent problem in clinical care, not limited to prescription narcotics, is easy access to all of the relevant information at the moment that it is needed. Prescribers need to digest an overwhelming amount of health information from each patient's EMR in order to provide care. One strategy developed and tested at a large health system, an effort led by 2 of the coauthors on this paper, was to build clinical-decision support into the workflow to deliver the necessary information to the prescriber at the point of care at the moment that the prescription for an opioid or a benzodiazepine is being written via a rule built into the EMR. The risk factors associated with misuse, abuse, and diversion of prescription opioids are complex and multifaceted (Table IV). A multidisciplinary team of physicians, researchers, administrators, and information-services personnel collaborated to identify a set of 5 risk characteristics (Table V) that are evidence-based, objective, and searchable in most medical record systems[98]. The algorithm and resulting alert were built using existing tools in the EMR rather than using proprietary software of any kind.

If 1 or more of the alert triggers are met, an alert "fires" in the EMR and presents the information to the prescriber (Fig. 1). The alert is concise, clear, and shows details regarding the triggers that are applicable to that particular patient[99]. Navigating the alert requires minimal time; the prescriber chooses to continue with the prescription as planned or to cancel the prescription.

We offer this as 1 example of a solution that can be implemented on a large scale to begin to stem the tide of prescription opioids. However, additional work needs to be done, including partnering with our state's PDMP to integrate the system into the EMR, providing guidelines and support for physicians to utilize opioid-sparing protocols for pain management for both acute and chronic pain, and providing treatment to those addicted to opiates. Examples of additional work being done on the national level and a list of resources are provided in Tables VI and VII, respectively.

TABLE VII Resources for Safe Opioid Prescribing*

Centers for Disease Control and Prevention Guideline for Prescribing Opioids for Chronic Pain: http://www.cdc.gov/drugoverdose/prescribing/guideline.html
Calculating Total Daily Dose of Opioids for Safer Dosage: http://www.cdc.gov/drugoverdose/pdf/calculating_total_daily_dose-a.pdf
Surgeon General's Turn the Tide Rx initiative: http://turnthetiderx.org
Criteria for Mandatory Enrollment or Query of PDMPs by State: http://www.pdmpassist.org/pdf/Mandatory_conditions.pdf

*PDMPs = Prescription Drug Monitoring Programs.

Conclusions

Musculoskeletal pain represents 1 of the most frequent reasons for opioids to be prescribed to patients. As the subject-matter experts in this arena, we should take a leadership role in improving prescribing safety and the stewardship of opioids. By understanding the evidence behind the medications used for pain relief, both opioid and nonopioid, we will become conversant in their appropriate usage. Additionally, by understanding other strategies for pain relief and system strategies for opioid safety, we can help lead the way to finding solutions to this opioid epidemic. ■

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