



# HHS Public Access

Author manuscript

*Drug Alcohol Depend.* Author manuscript; available in PMC 2017 August 14.

Published in final edited form as:

*Drug Alcohol Depend.* 2017 April 01; 173(Suppl 1): S22–S30. doi:10.1016/j.drugalcdep.2016.08.641.

## Targeting practitioners: A review of guidelines, training, and policy in pain management

Kelly S. Barth<sup>\*</sup>, Constance Guille, Jenna McCauley, and Kathleen T. Brady

Department of Psychiatry and Behavioral Sciences, College of Medicine, Medical University of South Carolina, Charleston, SC, United States

### Abstract

This paper reviews the current literature on clinical guidelines, practitioner training, and government/payer policies that have come forth in response to the national rise in prescription opioid overdoses. A review of clinical opioid prescribing guidelines highlights the need for more research on safe and effective treatment options for chronic pain, improved guidance for the best management of post-operative pain, and evaluation of the implementation and impact of guideline recommendations on patient risk and outcomes. Although there is increasing attention to training in pain management in medical schools and medical residency programs, educational opportunities remain highly variable, and the need for additional clinician training in the recognition and treatment of pain as well as opioid use disorder has been recognized. Mandated use of private, federal and state educational and clinical initiatives such as Risk Evaluation and Mitigation Strategies (REMS) and Prescription Drug Monitoring Programs (PDMPs) generally increase utilization of these initiatives, but more research is needed to determine the impact of these initiatives on provider behaviors, treatment access, and patient outcomes. Finally, there is an acute need for more research on safe and effective treatments for chronic pain as well as an increased multi-level focus on improving training and access to evidence-based treatment for opioid use disorder as well as non-pharmacologic and non-interventional chronic pain treatments, so that these guideline-recommended interventions can become mainstream, accessible, first-line interventions for chronic pain and/or opioid use disorders.

### Keywords

Pain; Guidelines; Training; Policy; Opioids

---

This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<sup>\*</sup>Corresponding author at: Department of Psychiatry & Behavioral Sciences, College of Medicine, Medical University of South Carolina 67 President Street, Charleston, SC 29425, United States.

#### Author contribution

All four authors performed literature reviews on selected topics and contributed to iterative drafts of manuscript writing. All authors read, contributed to, and approved the final manuscript.

#### Conflict of interest

No conflict declared.

## 1. Introduction

Chronic pain is complex and poorly understood, affecting approximately 20 million patients every year (Nahin, 2012). Although chronic pain can be managed with a variety of pharmacological and nonpharmacological interventions, most of these treatments have not been evaluated in long-term studies, and there is great heterogeneity in patient presentation, course of illness, and response to treatment in chronic pain. Front-line health care providers are challenged to choose the most feasible, effective and safe treatment for each patient with this complex illness within the time constraints of routine office visits with little quality evidence to guide them.

Two of the most commonly used medications for chronic pain are non-steroidal anti-inflammatory drugs (NSAIDs) and opioid pain medications. NSAIDs are widely taken and prescribed for the treatment of pain and inflammation in patients with various musculoskeletal conditions, with over 17% of people in the US reporting use of at least one NSAID in the past week (Kaufman et al., 2002). Prescription opioids are also commonly prescribed for pain. In 2012, US health care practitioners wrote more than 200 million prescriptions for opioids, double the number written in 1998, and 10 million more than in 2008 (Volkow, 2016). Although NSAIDs are associated with an array of potentially serious side effects and risks (Trelle et al., 2011), the increasing use of prescription opioids has been associated with an exponential rise in fatal opioid overdoses totaling more than 16,000 deaths per year (CDC, 2015). Because of this appreciable mortality risk with opioids, there has been a call for increased clinical guidance, training and mandates, aimed at practitioners prescribing opioids for pain. This paper will review the current literature on physician guidelines, practitioner training, and government/payer policies that have come forth in response to the national rise in opioid overdoses.

## 2. Clinical guidelines for chronic pain management with opioids

To address concerns about high rates of prescription opioid overdose, several organizations have developed clinical practice guidelines focused on improving the safe and effective opioid prescribing for chronic non-cancer pain. Although there is a paucity of quality research in the area of long-term pain management (including opioid use), there is a general consensus that given the high levels of opioid overdose, it is prudent to move forward with guidelines based on the best currently available evidence until more rigorous research data becomes available. Existing pain guidelines caution that most recommendations are based on systematic reviews of research with notable limitations (mostly observational trials) as well as expert assessment of different care options for chronic pain management. Guidelines emphasize that optimal clinical decision-making is based upon a clinician-patient relationship, taking into consideration each patient's unique needs and circumstances, and that recommendations are not to be taken as prescriptive standards of care (Dowell et al., 2016a).

### 2.1. Opioid prescribing guidelines for chronic pain, 2009–2012

There has been one systematic review of opioid prescribing guidelines to date. A 2014 “systematic review and critical appraisal” evaluated the quality and content of 13 eligible

pain guidelines published after 2008 addressing the use of prescription opioids for chronic pain in adults (Nuckols et al., 2014). The authors noted great variability in the quality of the opioid pain guidelines, which is not unusual compared with guidelines for other conditions such as breast cancer, migraine management, or mammography screening. However, compared with guidelines for other medical conditions, the opioid pain guidelines scored appreciably lower in the domain of “applicability,” which measures how the guidelines address likely barriers and facilitators of implementation of the recommendations, strategies to improve implementation of the recommendations, and resource implications of applying the recommendations. When the quality of the systematic review supporting each opioid pain guideline was evaluated, 10 of the 13 guidelines were found to be of poor or fair quality. Guidelines developed by the American Pain Society and the American Academy of Pain Medicine (Chou et al., 2009) and Canadian National Opioid Use Guideline Group (2010), had the highest quality scores. However, the authors note that even “the higher-quality guidelines generally relied on modest numbers of lower-quality observational studies for many recommendations” (Nuckols et al., 2014), a severe limitation common to all pain guidelines.

Despite variability in development methods, time range over which the guidelines were published, and the limited quality of evidence available, many of the evaluated guidelines made concordant recommendations about possible strategies for reducing risks of prescription opioids. This suggests clinical consensus on some measures, including: using caution with methadone, fentanyl, and higher doses of opioids (90–200 mg daily morphine milligram equivalent [MME]); titrating and switching opioids with caution; attention to drug-drug (particularly opioid-benzodiazepine) and drug-disease (e.g., sleep apnea and opioids) interactions; and incorporating office-based practices such as the use of risk assessment tools, treatment agreements, and urine toxicology for patients on opioids for chronic pain (Nuckols et al., 2014). The review suggested that developers of future opioid guidelines incorporate tools such as the GuideLine Implementability Appraisal tool (Chan, 2010) to address the barriers to guideline implementation and improve the “applicability” of opioid prescribing guidelines (Nuckols et al., 2014). They also called for future research to evaluate the effectiveness and impact of guideline recommendations on patient risk and patient outcomes, as there have been no evaluations of outcomes related to guideline implementation to date (Nuckols et al., 2014).

**2.1.1. CDC opioid prescribing guidelines, 2016**—Since publication of the review by Nuckols et al. (2014), the Center for Disease Control (CDC) has published an update to their Guidelines for Prescribing Opioids for Chronic Pain (Dowell et al., 2016a). Targeted at primary care clinicians, the CDC guideline makes 12 explicit recommendations: six are based on Type 4 evidence (clinical experience/observations; or observational or randomized controlled trials [RCTs] with several major limitations); four are based on Type 3 evidence (observational studies or RCTs with notable limitations); and one is based on Type 2 evidence (RCTs with important limitations or exceptionally strong evidence from observational studies). There was no Type 1 evidence available for this guideline (RCTs or overwhelming evidence from observational studies). The CDC guideline group based recommendations upon a clinical evidence review funded by the Agency for Healthcare

Research (Chou et al., 2012, 2015) on the risks and effectiveness of long-term (outcomes > 1 year) opioid therapy for chronic pain, as well as a “contextual review” of several topics published separately that supplemented the clinical evidence review and allowed outcomes of any duration (Dowell et al., 2016b). The contextual reviews streamlined the systematic review process by limiting searches and providing informal assessments of evidence quality (rather than an objective system of rating the quality of the research review). Although the authors caution that the rapid reviews “provide indirect evidence and should be interpreted accordingly” (Dowell et al., 2016a), this expedited approach was felt to be necessary given the public health urgency and need for opioid prescribing recommendations in a short time frame.

Of the 12 recommendations put forth by the CDC, the one supported with the highest level of evidence addresses the treatment of opioid use disorders (OUD): “Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder” (Dowell et al., 2016a). This is the only recommendation within the guideline based on Type 2 evidence, with the overall quality of the evidence rated as “moderate” (Dowell et al., 2016b). In the contextual review (Dowell et al., 2016b), the authors summarize four systematic reviews to support this recommendation: two evaluating methadone maintenance treatment *vs* non-replacement treatment (Fullerton et al., 2014; Mattick et al., 2009); one evaluating psychosocial and pharmacologic treatments *vs* pharmacologic (only) treatments for opioid detoxification (Amato et al., 2011); and one evaluating buprenorphine *vs* placebo or methadone for treatment of opioid use disorder (Mattick et al., 2014). Two reviews included participants who were heroin-dependent, and the other two reviews did not specify type of opioid dependency. Key findings of the reviews include: a moderate level of evidence of high treatment drop-out rates with opioid detoxification; high quality evidence that methadone maintenance treatment (MMT) is effective in decreasing illicit opioid use, improving treatment retention, and decreasing mortality; moderate quality evidence that MMT is effective in reducing criminal activity; and high quality evidence that buprenorphine is effective (no difference in efficacy *vs* MMT) in decreasing heroin use at doses of 16 mg or more, but less effective for treatment retention than MMT (Dowell et al., 2016b). The evidence for the effectiveness of buprenorphine in prescription OUD will be reviewed separately within this supplement.

In keeping with previous pain guidelines, the CDC guideline recommends the use of urine toxicology and prescription drug monitoring program (PDMP) data, acknowledging in the contextual review that clinicians do not consistently use these practices, education in data interpretation is needed, and there are risks with these practices (false positives, incorrect interpretation of data; Dowell et al., 2016b). Nonpharmacologic and nonopioid pharmacologic therapy for chronic pain are also still recommended, as there is some evidence for short-term effectiveness of these approaches, and they have less overdose risk than opioid therapy (Dowell et al., 2016b). Finally, these guidelines continue to recommend avoiding methadone, transdermal fentanyl, and concurrent prescriptions of benzodiazepines and opioids.

In contrast with some previous pain guidelines, CDC guidelines do not explicitly suggest a written patient-provider agreement, but rather suggests setting treatment goals, detailing treatment expectations, and discussing alternatives/risks/benefits of opioids. Additionally, using a 1 year outcomes criteria to evaluate the benefits of opioid therapy, no studies qualified for the clinical evidence review, leading to the conclusion that, “No evidence shows a long-term benefit of opioids in pain and function vs no opioids for chronic pain with outcomes examined at least 1 year later (with most placebo-controlled randomized clinical trials  $\leq$  6 weeks in duration)” (Dowell et al., 2016a). This is a notable change in language from previous pain guidelines, which included studies with outcomes less than 1 year and concluded that “chronic opioid therapy can be an effective therapy for carefully selected and monitored patients with CNCP [chronic non-cancer pain]” (Chou et al., 2009). Lastly, based on Type 3 evidence (Edlund et al., 2014; Dunn et al., 2010; Gomes et al., 2011a, 2011b, 2013), the CDC guidelines recommended reassessing individual benefits and risks of opioids at doses of “50 morphine milligram equivalent [MME] or more per day, and should avoid increasing dosage to 90 [MME] or more per day or carefully justify a decision to titrate dosage to 90 [MME] or more per day” (Dowell et al., 2016a). This was a significant decrease from previous guideline-recommended risk threshold of 90–200 MME (Nuckols et al., 2014).

Other new CDC guideline recommendations include using immediate release opioids when initiating opioid treatment, using a validated pain scale, avoiding combination of immediate-release and long-acting opioids and offering naloxone for overdose reversal to high-risk patients (Dowell et al., 2016a).

## 2.2. Summary

Given the continued high rates of opioid prescribing despite the large number of deaths related to opioid use, the most recent pain guidelines send a clear, strong message to prescribers about the risks of prescription opioids. Pain guidelines to date have been hindered by the paucity of quality clinical research in the area of pain management and must be interpreted and implemented within the context of the appreciable limitations of the data on which they are based. These recommendations should not be interpreted as a standard of care. However, given the pressing public health problem of inappropriate opioid use and overdose, there is a clear need for consensus and guidance for front-line clinicians on risk reduction measures that can be implemented now while more rigorous studies are completed.

Of the available treatments for chronic pain reviewed in opioid guidelines, non-pharmacologic treatments such as cognitive-behavioral therapy, exercise therapy, and biopsychosocial rehabilitation appear to offer the most promise with the least amount of risk (Dowell et al., 2016b). However, these modalities can be difficult to access from a logistic and financial standpoint, particularly for those of low socio-economic status, a group at particular risk for overdose (Gomes et al., 2011b). When evaluating pharmacologic options for the management of chronic pain, the treatment of neuropathic pain and fibromyalgia with anticonvulsants and SNRIs appears to be effective with a good risk:benefit ratio (Dowell et al., 2016b). For the management of other chronic pain conditions, such as chronic back pain,

the risk:benefit ratio for pharmacologic options is less clear (Dowell et al., 2016b; Schnitzer et al., 2004; Urquhart et al., 2008). As opioid guidelines are primarily intended to provide guidance on opioid use, the role of interventional and surgical management of chronic pain conditions are generally not reviewed. However, a critical review of the long-term effectiveness of all non-opioid options for the treatment of chronic pain is warranted, as decreasing the use of opioids in an attempt to decrease overdose mortality does not address the pressing clinical issues for the individual patient and primary care physician regarding the paucity of effective long-term treatments for chronic pain.

Aside from the great need for better quality research in chronic pain management, opioid pain guidelines also highlight the need to evaluate the effects of guidelines on clinical practice behaviors and patient outcomes, including overdose mortality, opioid abuse, access to care and medications, and pain and functional measures. There is also a call to improve the applicability of guidelines by pre-emptively addressing barriers to implementation, using items such as the GuideLine Implementability Appraisal tool (Chan, 2010). Finally, policy-makers and payers must improve access to the non-opioid therapies and treatment for opioid use disorder and funding agencies must support more research on long-term treatment options for chronic pain.

### 3. Clinical guidelines for post-operative pain management

#### 3.1. Post-operative opioid pain management

Post-operative pain is an anticipated outcome following a surgical procedure with 80% of patients experiencing post-operative pain and approximately 75% describing moderate-to-very severe pain intensity (Apfelbaum et al., 2003; Gan et al., 2014). Opioid medications are commonly prescribed as part of a multimodal postoperative pain management strategy. However, despite expert consensus recommending tapering of these medications following a surgical procedure, there are no studies to date that provide guidance on the optimal method for opioid cessation following surgery (Chou et al., 2016). This may, in part, be due to the fact that there is significant variability in surgical procedures and anticipated recovery times (e.g., invasive vs. non-invasive, traumatic vs. elective), individual variability in patient health characteristics (e.g., young and healthy vs. older with multiple chronic diseases) and factors that impact drug metabolism (e.g., opioid naïve vs. opioid tolerant). However, without some sort of prescribing guidelines there is likely a tremendous amount of variability in post-surgical opioid prescribing practices and little is known about the risks and benefits of tapering strategies.

Recently, the American Pain Society, in collaboration with the American Society of Anesthesiology and American Society of Regional Anesthesia and Pain Medicine, published guidelines on the management of post-operative pain including transition to outpatient care following surgery (Chou et al., 2016). Despite an extensive review of the literature, they found only anecdotal reports and clinical experience to guide providers in post-operative opioid cessation strategies.

Based on limited literature, the main strategies recommended for post-operative opioid cessation were patient and family discharge education related to the safe use, cessation and

disposal of opioid medications and clarity around the patient's transition back to their medical home (Chou et al., 2016). Key treatment team members involved in these discussions can include prescribers, nurses, physical or occupational therapists and pharmacists. The treatment team should provide information to the patient and caregivers about potential risks associated with opioid medications including common side effects like constipation, sedation, withdrawal symptoms with abrupt discontinuation as well as risk for addiction and unintentional overdose and death, especially when opioids are combined with other central nervous system depressants including alcohol or benzodiazepines (Chou et al., 2016; Dowell et al., 2016a). Discharge teaching should include a plan for reduction and discontinuation of opioid medication as pain and functioning improve. Although there is insufficient evidence to support recommendations on how to best taper opioids, in general, experts recommend that for patients using opioid for one-two weeks, dose reduction by 20–25% every 1–2 days should be sufficient to prevent withdrawal symptoms (Chou et al., 2016). Similarly, there is insufficient evidence to support recommendation on when to best taper opioids post-surgically and experts highlight the need for individualized treatment plans for patients. Patient's chronically prescribed opioids prior to surgery should also be instructed on how to taper their post-operative opioid medications to their pre-operative maintenance dose, but there is a paucity of evidence to support recommendations on when or how to best taper these medications (Huxtable et al., 2011; Shah et al., 2015).

For opioid tolerant patients, pre-operative planning is critical and it should be anticipated that they will require larger doses of opioid medications to control their operative and post-operative pain, compared to opioid-naïve patients. A theoretical and controversial practice includes lowering the pre-operative dose of opioid medication in opioid-tolerant patients one to two weeks prior to surgery so that opioid tolerance is reduced and thus less opioid medication is needed operatively or post-operatively to manage pain. However there is a paucity of data to support this practice as well as the increased potential for uncontrolled post-operative pain.

**3.1.1. Post-operative dental pain**—Dentists prescribe 8% of the opioids in the U.S. totaling 18 million prescriptions a year, second only to primary care physicians (Governale, 2010). These opioid prescriptions are most often directed at the management of acute and post-operative pain, but over 25% of the prescriptions dentists write for chronic pain are opioids (Ringwalt et al., 2014). Notably, this rate of prescribing occurs despite there being fair evidence for the effectiveness of non-opioid dental treatments, including surgical interventions (Hargreaves and Baumgartner, 2002), mandibular long-acting anesthetic injections (Gordon et al., 1997, 2010), pre-operative and post-operative NSAIDs (which have been shown to be as effective as opioids for many (Hersh et al., 2011), and pre-procedural analgesics (acetaminophen; Denisco et al., 2011). An important dental population exposed to opioids include the 5 million people per year undergoing 3rd molar extraction (Becker, 2010). This prophylactic procedure is responsible for approximately 3.5 million young adults being exposed to opioid pain medications per year (Friedman, 2007), though systematic reviews and randomized-controlled trials have shown combination therapy with ibuprofen and acetaminophen to be more effective than either agent alone and as effective as opioid-acetaminophen combinations with fewer side effects (Moore and Hersh, 2013). The

only dental pain management guideline available is the 2015 Pennsylvania Guideline on the Use of Opioids in Dental Practice (Pennsylvania Dental Association, 2015). This guideline is not based on a systematic review, but references the APS-AAPM Pain Guidelines (Chou et al., 2009) and recommends (1) NSAIDs and non-opioid analgesics as first line treatments for acute dental pain (with appropriate attention to risks); (2) use of the state's prescription monitoring program; (3) not prescribing more opioids than needed; (4) educating about safe disposal of unused medications (a particular risk for dental patients); and (5) avoiding long-acting opioids, opioids with benzodiazepines or opioid use in patients with obstructive sleep apnea (Pennsylvania Dental Association, 2015). Given the relatively clear risk: benefit advantage of non-opioid treatments for the management of acute and post-operative dental pain and the high rates of opioid use in dental medicine, a formal systematic review and evidence-based guideline development could have a high-impact in an at-risk population.

**3.1.2. Post-operative pain in opioid use disorders (OUDs)**—Opioid agonist therapies such as methadone or buprenorphine are effective treatments for patients with OUDs. Both the anesthesia and psychiatric literature have highlighted the clinical challenges to treating post-operative pain in patients with OUDs on maintenance medications including high opioid tolerance (Gutstein and Akil, 2001; Fishman et al., 2002; Johnson et al., 2005; Walsh and Eissenberg, 2003), opioid cross-tolerance (Collett, 1998; Doherty et al., 2001; Houtsmuller et al., 1998), heightened pain sensitivity due to hyperanalgesia (White, 2004; Alford et al., 2006), licit and illicit drug use (Hwang et al., 2015; Huxtable et al., 2011; Shah et al., 2015) and conflicting attitudes about pain and addiction treatment held by patients and medical providers (Alford et al., 2006). Unfortunately, few studies have systematically evaluated the efficacy of post-operative pain treatment strategies for those maintained on methadone or buprenorphine. In a recent review of this topic, pain treatment in this population has largely been guided by case reports, retrospective reviews, pharmacological principles, clinical experience and expert opinion (Eyler, 2012). Overall recommendations are similar to treating those with general opioid tolerance, including the need to use larger amounts of opioids for longer periods of time to adequately treat acute post-operative pain (Mitra and Sinatra, 2004; Lewis and Williams, 2005; Mehta and Langford, 2006; Vadivelu et al., 2016; Dale et al., 2016). Similar to opioid-tolerant patients, there are no controlled studies to guide the specifics of these recommendations for patients with OUDs (Eyler, 2012), an important area for future investigation. Currently, efforts are underway to develop evidence-based best practices and guidelines for opioid tolerant patients undergoing surgery including those with OUDs receiving agonist therapy (Dykstra, 2014).

One issue debated in the extant literature that may differentiate the management of post-operative pain in those with OUDs receiving maintenance medication, compared to opioid tolerant patients treated for pain conditions, is physician concern that use of these medications will result in relapse to drug use (Alford et al., 2006; Collins and Streltzer, 2003; Wolfred et al., 2009). Unfortunately there are few studies that address this concern. One small retrospective study conducted among methadone maintenance patients found that those who received post-surgical opioids following surgery were not at greater risk of relapse, compared to matched controls receiving methadone but not undergoing surgery and acute pain management (Kantor et al., 1980). Studies evaluating the risk of relapse to drug



use due to prescribing opioid for post-operative pain management are sparse and limited by small sample sizes. An increased understanding of actual risk of relapse and potential strategies to minimize this risk in individuals on opioid agonist therapy experiencing post-operative pain are greatly needed.

Another theoretical issue is the fact that buprenorphine can potentially present additional pain management challenges due to its high affinity and slow dissociation at the mu opioid receptor making it more difficult to provide adequate pain control with other opioid agonist therapies (Alford et al., 2006; Vadivelu et al., 2016). However, data to support this claim is conflicting, with case reports demonstrating adequate post-operative pain control with the use of additional opioid therapies in those on buprenorphine maintenance (Alizadeh et al., 2015) and other case reports demonstrating inadequate post-operative pain control (Alford et al., 2006). Determining the efficacy of post-operative pain management strategies for patients maintained on buprenorphine is another important line of investigation.

Women in labor and delivery with OUDs on opioid maintenance medications are a subpopulation of patients where more extensive clinical research is available to evaluate the efficacy of post-operative pain management. In one study including 68 pregnant methadone-maintained women, there were no differences, compared to controls, in intrapartum pain or analgesia use (Meyer et al., 2007). After vaginal delivery, methadone-maintained women experienced more pain, compared to controls, but there were no differences in opioid use. Following a cesarean delivery, methadone-maintained women had similar pain experiences and perioperative analgesic needs, compared to controls, but required 70% more opioid analgesic after cesarean delivery. These findings are similar to another study of 63 pregnant buprenorphine-maintained women who had similar intrapartum pain and analgesic needs during labor, increased pain but no increase in analgesia use following vaginal delivery, but experienced more postpartum pain and required 47% more opioid analgesia following a cesarean delivery, compared to matched controls (Meyer et al., 2010). Lastly, one study compared pain experiences and analgesia use among pregnant buprenorphine maintained (n = 8) and methadone-maintained (n = 10) pregnant women and demonstrated that both groups had similar and adequate postpartum pain control with opioid and non-opioid medication (i.e., Ibuprofen; Jones et al., 2009). Differences between these two groups were found in the use of Ibuprofen with the buprenorphine group decreasing their dose of ibuprofen and the methadone group increasing their dose over time. Limited data support the clinical recommendations to continue maintenance medications in pregnant women during and after labor and delivery while providing additional opioid and non-opioid pain medications at higher doses than typically used for opioid naïve pregnant women.

In summary, post-operative clinical pain guidelines suggest that providers should not continue opioid medications beyond post-surgical pain or if pain persists beyond the expected period of time, but there are no clear guidelines on what the appropriate timing for tapering opioids post-operatively. Currently, clinical guidelines suggest that there is 'no one size fits all' approach to the management of post-operative pain, but clinicians should balance concerns of minimizing suffering and maximizing rehabilitation while managing the potential for unintentional consequences of these medications (Bourne, 2010; Alford et al., 2006; Mitra and Sinatra, 2004; Lewis and Williams, 2005; Mehta and Langford, 2006).

There is increased need for data to guide the development of post-operative pain guidelines and guidelines to address sub-specialty populations such as dental patients, peri-partum patients, and opioid tolerant patients with and without opioid use disorders.

#### 4. Clinician training in pain management and substance use disorders

The issues surrounding opioid prescribing in the United States have also brought attention to the education of physicians and other healthcare providers in the management of pain and the recognition and treatment of substance use disorders (SUDs). A survey of Kaiser Permanente's clinical department chiefs for internal medicine, pediatrics, general surgery, and obstetrics/gynecology conducted in 2010 noted a deficiency in newly trained physicians in the management of chronic pain (Crosson et al., 2011). A 2010 National Pain Summit (Lippe et al., 2010) concluded that medical education in the field of pain was inadequate and needed to be strengthened in scope, content, and duration. In response to the opioid epidemic, medical schools across the country have implemented changes in their curriculum to include a greater focus on pain management, opioid prescribing and SUDs. A national survey of primary care physicians and adults receiving care for substance use disorders found that more than 50% of patients reported that their physicians did not address their SUDs and only 25% were involved in their decision to seek treatment while less than 20% of primary care physicians considered themselves prepared to identify alcohol or drug dependence (CASA, 2000). Using data collected from the 2009–2010 Liaison Committee on Medical Education (LCME), the accrediting body for medical education programs, only 80% of U.S. medical schools required 1 or more pain sessions, while twice as many sessions were required in 92% of Canadian medical schools (Mezei et al., 2011). In the LCME survey for 2014–2015, 136 of 141 medical schools reported that content on SUDs and pain management was included in required coursework, suggesting a great increase (Association of American Medical Colleges, 2016). The Association of American Medical Colleges estimates that 93% of US medical schools planned or implemented changes in curriculum to address opiates, pain and SUDs in the last 5 years. For example, in the state of Massachusetts, four medical schools worked with the state medical society to develop a set of 10 core competencies in pain management and addiction which have been integrated across the 4 years of medical school training through experiential and didactic training (O'Rourke, 2016).

Residency programs provide another opportunity for training in pain management and the treatment of substance use disorders (SUDs). A survey conducted in 2000 found that only 56.3% of medical subspecialty residencies requiring SUD training with curricular hours ranging from 3 in emergency medicine and obstetrics and gynecology to 12 in family medicine (Isaacson et al., 2000). A number of SUD training initiatives for primary care residents have been developed, evaluated and found to be effective (Polydorou et al., 2008), but SUD training is not required and therefore not consistently available in primary care residency programs. However, beginning in 2001, general psychiatry residency programs were required to provide a 1-month training experience in addictions to all residents (ACGME, 2016). In addition, physicians who have completed a residency in psychiatry can pursue certification in Addiction Psychiatry through an ACGME-accredited fellowship program. In March, 2016, Addiction Medicine was recognized as a new subspecialty under

the American Board of Preventive Medicine (ABPM), allowing primary care physicians and physicians from other medical specialties to pursue certification in Addiction Medicine.

In terms of pain management training in residency, a survey of physicians practicing in 2000 found that although only 10% reported receiving formal training in pain management during residency, younger physicians were more likely have received training, suggesting that there may be increasing attention to training in pain management in some residency programs (Green et al., 2001). Accredited post-graduate fellowship training in pain medicine is available for specialists in select fields, such as anesthesiology, neurology, psychiatry and rehabilitation medicine (Lippe et al., 2010), but not for general practitioners. There are multiple on-line and face-to-face courses in pain management targeting physicians offered by Universities, for-profit CME companies and professional organizations, but participation in these post-graduate training forums is variable.

The need for physician training in pain management and recognition and treatment of SUDs has been recognized as one element that can improve the opioid crisis in the United States and lead to better patient care. However, this is a long-term solution that is not likely to have an immediate impact. Careful evaluation of the educational programs that have been introduced will be important to setting standards for training in these critical areas in the future.

## 5. Policy impacting physician guidelines and training

Physician guidelines and training for pain management have historically been impacted by federal and state legislative efforts, as well as payer-issued policies and mandates such that policy codifies guidelines and/or promotes or mandates training deemed necessary to comply with a given policy (Brennan, 2015). As national attention to the rise in prescription opioid abuse and overdose has grown, the majority of these policy efforts have focused on the appropriate use of prescription opioids for pain management with the aim of balancing adequate pain management with mitigation of risks associated with the use of prescription opioids (Brennan, 2015; Hill, 1996; Manchikanti et al., 2016). In 2011, the Office of National Drug Control Policy (ONDCP, 2011) first directly addressed the prescription opioid abuse epidemic in its National Drug Control Strategy. Updated annually, the National Drug Control Policy has focused recommendations on four strategic components: (1) educating patients, providers, youth, and parents regarding the dangers of nonmedical opioid use and diversion, as well as educating health-care providers about pain medicine prescribing; (2) enhancing and supporting prescription drug monitoring efforts; (3) ensuring proper disposal through increased prescription return/drug take-back programs and drug deactivation systems; and (4) enhancing enforcement (ONDCP, 2015). The following section will provide a brief overview of major federal, state, and payer policies that currently impact physician prescribing guidelines and training pertinent to the use of opioids for pain management.

### 5.1. Federal policy

Policy initiatives of enforcement and education have traditionally been executed primarily by two federal agencies – the Drug Enforcement Agency (DEA) and the Food and Drug

Administration (FDA) that together determine the schedule of specific prescription opioid formulations (Stayner and Copenhaver, 2012). In addition, the DEA is responsible for licensing physicians and eligible healthcare providers to prescribe controlled substances and has primary, though not exclusive, authority to prevent, detect, and investigate the diversion of controlled substances by healthcare prescribers (Good, 1998). The FDA is also responsible for assuring the safety, efficacy, and security of human drugs via their approval process, as well as for implementing post-marketing monitoring of drug safety and providing accurate, evidence-based information regarding the safest use of medicines to the general public.

In 2012, the FDA exercised its authority to require single shared Risk Evaluation and Mitigation Strategies (REMS) program from drug manufacturers of extended release/long acting (ER/LA) opioids (FDA, 2016). REMS were intended to help balance the risk/benefit profile of certain opioid medications by requiring manufacturers to provide training and education to physicians regarding universal precautions in opioid prescribing, updated medication guides for each product, and patient counseling documents (Nicholson et al., 2012; Stanos, 2012). It is important to note that REMS requirements mandate that drug manufacturers produce educational materials for specified products; however, there is no accompanying mandate to ensure dissemination of these educational products amongst prescribing physicians. As such, prior REMS programs have suffered low physician participation rates and failed to demonstrate desired effects on prescribers' knowledge (Brooks, 2014; FDA, 2014; Woodcock, 2009). In response, the ER/LA REMS program was the first to leverage prescriber trainings offered through existing, accredited continuing education (CE) providers (Center for Health Policy, 2015). REMS-compliant CE modules are required to cover all elements of the FDA Blueprint for Prescriber Education for ER/LA Opioids, include a knowledge assessment component, and be subject to independent audit (FDA, 2012). Despite documented performance targets for prescriber training, to date the execution and effectiveness of ER/LA class REMS physician training/education has not been systematically evaluated (Center for Health Policy, 2015; Rodriguez-Monguio et al., 2014).

## 5.2. State policy

The majority of policy influencing pain management recommendations and impacting opioid prescribing has been enacted at the level of state government. An increasing number of state governments and medical licensing boards have mandated some level of physician CE focused on pain management (American Medical News, 2012); however, a recent systematic legal analysis of state CME requirements reported that only five states require most or all prescribers to complete such CE courses and fewer than half of all states require CE from any prescribers (Davis and Carr, 2016). One of the common themes of state legislation includes expansion of naloxone access for overdose treatment (National Conference of State Legislations, 2014). Naloxone expansion policies have been enacted in 43 states and Washington D.C. (Davis and Carr, 2015), yet despite the prevalence and effectiveness of naloxone expansion policies, prescription status and cost of naloxone remain notable barriers to widespread uptake, even in states with laws targeting expansion of naloxone access (Clark et al., 2014; Coffin and Sullivan, 2013; Davis and Carr, 2015; Haegerich et al., 2014).

States have also enacted PDMP policies with the intention of promoting balance between adequate pain management options and prevention of harms associated with abuse of prescription opioids. PDMPs vary notably from state to state with respect to statement of purpose (e.g., overdose prevention, reduction of diversion, etc.), technical functionality, and laws regarding intended benefits (Davis et al., 2015; Haffajee et al., 2015). To date, nearly all evaluations of PDMP effects are observational, and findings regarding PDMP effectiveness in impacting proximal outcomes (e.g., promoting physician confidence in prescribing decisions, enhanced detection of abuse and diversion), as well as more distal outcomes (e.g., reducing overall prevalence of diversion and overdose) remain mixed (Griggs et al., 2015; Haegerich et al., 2014; Kolodny et al., 2015; McAllister et al., 2015; Rutkow et al., 2015; Reifler et al., 2012; Surratt et al., 2014; Thomas et al., 2014; Green et al., 2015). Physician awareness, registration, and use of PDMPs generally remain low (Haffajee et al., 2015); however, mandated registration and use policies adopted by a growing number of states have demonstrated the potential to increase registration and use of PDMPs, resulting in subsequent reductions in doctor shopping, as well as reductions in the prescribing of some commonly abused opioids (PDMP Center of Excellence, 2014). Of note, some recent evidence suggests that these policies may have unintended consequences that impact the availability of opioids as a pain management option (Larrat et al., 2014; Scholten and Henningfield, 2016; Webster, 2013). In addition to the potential undue training and practice burden being placed on physicians, it has been suggested enhanced monitoring of physician prescribing behavior may have unintended downstream consequences, including limiting physician and patient options for management of chronic pain via decreased access to prescription opioids, which, in combination with lack of access to effective identification and treatment of addiction, may be contributing to documented increases in heroin use (Delcher et al., 2015). However, research in this area is generally correlative in nature and limited. Additional efforts are necessary to evaluate and the benefit-risk balance of the wide array of PDMP policies being implemented from state to state.

### 5.3. Insurer/payer policy

Insurers – particularly Centers for Medicare and Medicaid Services (CMS) – have begun efforts to leverage their medical and pharmacy claims data to identify “inappropriate” prescribing and potential prescription drug abuse by patients (Haegerich et al., 2014; Keast et al., 2015). Patient review and restriction (i.e., lock-in), drug utilization review, prior authorization, and medicine quantity limits have been recommended as mechanisms for altering physician and patient behavior (Keast et al., 2015; Shoemaker et al., 2010). Research evaluating the effectiveness of these strategies is scant and largely focused on outcomes of cost savings and healthcare utilization; however, the limited available evidence regarding insurer strategy impact on prescribing and use behavior does indicate promise (Haegerich et al., 2014; Keast et al., 2015). Additional research is needed to enhance the quality of evidence by assessing the impact of insurer strategies on clinician pain management practices using appropriate comparison groups, including of long-term follow-up, and controlling for potential confounds.

## 6. Conclusions

As the high rates of prescription opioid overdoses continue in the United States, there is increased scrutiny on practitioners as the primary source of prescription opioids fueling this crisis. The CDC opioid prescribing guidelines are an essential step forward in highlighting the risks of opioid-based treatment in a poorly-understood condition that has a paucity of quality evidence about effective long-term treatment options. At the same time, efforts from state and federal policy-makers and payers have attempted to address this problem through voluntary and mandated physician education, required PDMP use, medication quantity limits, and naloxone access for overdose treatment. However, the effectiveness of guidelines and mandates on changing physician behavior or the impact on patient outcomes has not been well evaluated (Hwang et al., 2015; Lewis et al., 2014; Starrels et al., 2010).

Additionally, as more training and practice burden is placed on primary care practitioners to care for this complex patient population, it is unknown what effects the mandates, payer policies, and guidelines will have on clinician interest or feasibility to care for chronic pain patients, particularly those on opioids. Within the specialty medical areas, particularly post-surgical pain management, guidelines encouraging efforts to decrease the use of post-operative opioids when evidence-based (i.e., for dental procedures) and prevent the transition from acute opioid management to chronic opioid management could have outcomes that benefit both individual patients and the public at large.

While one of the results of recent guidelines and mandates will be a decrease in overall rates of opioid prescribing in the United States, it is not known what the impact of the decreased availability of opioids will have on patient pain and functional outcomes, addiction rates, or overdose deaths. As the pendulum swings away from opioid management for chronic pain, there continues to remain little evidence for effective long-term non-opioid chronic pain management options (outside of neuropathic pain), and limited access to specialty referrals for non-procedural, non-opioid pain management, including guideline-recommended non-pharmacologic treatments for chronic pain such as biopsychosocial rehabilitation, exercise therapy and cognitive behavioral therapy. There is an acute need for more research on safe and effective treatments for chronic pain as well as an increased multi-level focus on improving access to these non-pharmacologic and non-interventional treatments, so that these treatments, that tend to be more time-intensive and less-well reimbursed, can become mainstream, first-line interventions for chronic pain.

It is important to highlight the area of highest quality evidence in current pain guidelines, which are the effective treatments available for opioid use disorders (OUDs). Improving patient awareness of the treatments available for OUDs, decreasing stigma provider education about the recognition and management of OUDs, and reducing financial and logistical barriers to addiction care will improve access to life-saving treatments that could have the most immediate impact on opioid overdose mortality. Meanwhile, implementing other policy- and guideline-recommended risk-reduction measures, such as avoiding high risk opioid medications (e.g., methadone, fentanyl), avoiding high risk medication combinations (e.g., opioids and benzodiazepines), monitoring the risks of higher opioid doses, and checking state prescription databases are steps that all providers can take now to attempt to improve the safety of their patients on opioids, while researchers, policy-makers,

and payers work towards long-term solutions for this national problem. As guidelines cannot take into account the individualized risk:benefit ratio for every patient, ultimate clinical decision-making comes back to the front-line providers, who have been challenged to overcome a multitude of barriers in improving individual patient-centered outcomes for people with this complex condition within the constraints of routine ambulatory care.

## Acknowledgments

### Role of funding source

The efforts of Drs. Barth (1K23 DA039328-01A1), Guille (1K23DA039318-01), and McCauley (1K23 DA036566-01A1) are funded by the National Institute on Drug Abuse. Dr. Brady's effort is funded by R25 DA020537, UL1 TR00006205S1, P50 DA016511, U10 DA01372, and K12 HD055885. The funding sources had no role in the preparation or writing of this review manuscript.

## References

- AAMC Newsroom. [Accessed on May 19 2016] Medical Schools Address Opioid Epidemic Through Innovations in Curricula and Other Methods, Capitol Hill Briefing Shows. 2016. at [https://www.aamc.org/newsroom/newsreleases/453800/20160201\\_medicalschooolsaddressopioidepidemicthroughinnovationsi.html](https://www.aamc.org/newsroom/newsreleases/453800/20160201_medicalschooolsaddressopioidepidemicthroughinnovationsi.html)
- Accreditation Council of Graduate Medical Education (ACGME). [Accessed on August 30 2016] ACGME Program Requirements for Graduate Medical Education in Psychiatry. 2016. website. Available at [https://www.acgme.org/Portals/0/PFAssets/ProgramRequirements/400\\_psychiatry\\_2016.pdf](https://www.acgme.org/Portals/0/PFAssets/ProgramRequirements/400_psychiatry_2016.pdf)
- Alford DP, Compton P, Samet J. Acute pain management for patients receiving maintenance methadone or buprenorphine therapy. *Ann Intern Med.* 2006; 144(127):127–134. [PubMed: 16418412]
- Alizadeh S, Mahmoudi GA, Solhi H, Sadeghi-Sedeh B, Behzadi R, Kazemifar AM. Post-operative analgesia in opioid dependent patients: comparison of intravenous morphine and sublingual buprenorphine. *Addict Health.* 2015; 7(1–2):60–65. [PubMed: 26322212]
- Amato L, Minozzi S, Davoli M, Vecchi S, Ferri MM, Maynet S. Psychosocial and pharmacological treatments for opioid detoxification. *Cochrane Satabase Syst Rev C.* 2011:CD005031.
- American Medical News. Hot-Button Issues Drive State CME Mandates. 2012. (Retrieved April 10 2016), from <http://www.amednews.com/article/20120213/profession/302139947/2/-minb>
- Apfelbaum JL, Chen C, Mehta SS, Gan TJ. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. *Anesth Analg.* 2003; 97:534–540. [PubMed: 12873949]
- Becker DE. Pain management: part 1: Managing acute and postoperative dental pain. *Anesth Prog.* 2010; 57:67–79.
- Bourne N. Acute pain management in the opioid-tolerant patient. *Nurs Stand.* 2010; 25:35–39.
- Brennan F. The US congressional decade on pain control and research 2001–2011: a review. *J Pain Palliat Care Pharmacother.* 2015; 29:212–227. [PubMed: 26458017]
- Brooks MJ. Mitigating the safety risks of drugs with a focus on opioids: are risk evaluation and mitigation strategies the answer? *Mayo Clin Proc.* 2014; 89:1673–1684. [PubMed: 25441401]
- CASA. Missed Opportunity National Survey Of Primary Care Physicians And Patients On Substance Abuse. National Center On Substance Abuse At Columbia University; New York: 2000.
- Center for Health Policy. Incorporating Continuing Education into Single-Drug REMS: Exploring the Challenges and Opportunities. Brookings Institute; Washington, DC: 2015.
- Centers for Disease Control and Prevention. Number and age-adjusted rates of drug-poisoning deaths involving opioid analgesics and heroin: United States, 2000–2014. 2015.
- Chan, W. [Accessed on May 19 2016] Implementation of GLIA assessment in Kaiser Permanente and NHLBI to improve implementability of recommendations. *Otolaryngol. Head Neck Surg.* 143,

GuideLine Implementability Appraisal Website. 2010. at <http://nutmeg.med.yale.edu/glia/login.htm?jsessionid=C839F08F4060F49D3F86DF9D7A749BA>

- Chou R, Fanciullo GJ, Fine PG, Adles JA, Ballantyne JC, Davies P, Donovan MI, Fishbain DA, Foley KM, Fudin J, Gilson AM, Kelter A, Mausekoff A, Co'Connor PG, Passik SD, Pasternak GW, Portenoy RK, Rich BA, Roberts RG, Todd KH, Miaskowski C. American Pain Society-American Academy of Pain Medicine Opioids Guidelines Panel. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain*. 2009; 10:113–130. [PubMed: 19187889]
- Chou, R., Deyo, R., Devine, B., Hansen, R., Sullivan, S., Jarvik, JG., Blazina, I., Dana, T., Bougatsos, C., Turner, J. Evidence Report/Technology Assessment No. 218. (Prepared by the Pacific Northwest Evidence-based Practice Center Under Contract No. 290-00014-I). AHRQ (Agency for Healthcare Research and Quality); Rockville, MD: 2012. The Effectiveness and Risks of Long-Term Opioid Treatment of Chronic Pain. Publication No. 14-E005-EFat <http://www.ahrq.gov/research/findings/evidence-based-reports/opioidstp.html> [Accessed on May 19 2016]
- Chou R, Turner JA, Devine EB, Hansen RN, Sullivan SD, Blazina I, Dana T, Bougatsos C, Deyo RA. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Ann Intern Med*. 2015; 162:276–286. [PubMed: 25581257]
- Chou R, Gordon DB, de Leon-Casasola OS, Rosenberg JM, Bickler S, Brennan T, Carter T, Cassidy CL, Chittenden EH, Degenhardt E, Griffith S, Manworren R, McCarberg B, Montgomery R, Murphy J, Perkal MF, Suresh S, Sluka K, Strassels S, Thirlby R, Viscusi E, Walco GA, Warner L, Weisman SJ, Wu C. Management of postoperative pain: a clinical practice guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. *J Pain*. 2016; 17:131–157. [PubMed: 26827847]
- Clark AK, Wilder CM, Winstanley EL. A systematic review of community opioid overdose prevention and naloxone distribution programs. *J Addict Med*. 2014; 8:153–163. [PubMed: 24874759]
- Coffin PO, Sullivan SD. Cost-effectiveness of distributing naloxone to heroin users for lay overdose reversal. *Ann Intern Med*. 2013; 158:1–9. [PubMed: 23277895]
- Collett BJ. Opioid tolerance: the clinical perspective. *Br J Anaesth*. 1998; 81:58–68. [PubMed: 9771273]
- Collins ED, Streltzer J. Should opioid analgesia be used in the management of chronic pain in opiate addicts? *Am J Addict*. 2003; 12:93–100. [PubMed: 12746085]
- Crosson FJ, Leu J, Roemer BM, Ross MN. Gaps in residency training should be addressed to better prepare doctors for a twenty-first-century delivery system. *Health Aff*. 2011; 30:2142–2148.
- Dale R, Chen T, Ballantyne J. Planning for perioperative pain management. *Hosp Med Clin*. 2016; 5:303–318.
- Davis CS, Carr D. Legal changes to increase access to naloxone for opioid overdose reversal in the United States. *Drug Alcohol Depend*. 2015; 157:112–120. [PubMed: 26507172]
- Davis CS, Carr D. Physician continuing education to reduce opioid misuse, abuse, and overdose: many opportunities few requirements. *Drug Alcohol Depend*. 2016; 163:100–107. [PubMed: 27137406]
- Davis CS, Johnston JE, Pierce MW. Overdose epidemic, prescription monitoring programs, and public health: a review of state laws. *Am J Public Health*. 2015; 105:e9–e11.
- Delcher C, Wagenaar AC, Goldberger BA, Cook RL, Maldonado-Molina MM. Abrupt decline in oxycodone-caused mortality after implementation of Florida's Prescription Drug Monitoring Program. *Drug Alcohol Depend*. 2015; 150:63–68. [PubMed: 25746236]
- Denisco RC, Kenna GA, O'Neill MG, Kulich RJ, Moore PA, Kane WT, Mehta NR, Hersh EV, Katz NP. Prevention of prescription opioid abuse – the role of the dentist. *J Am Dent Assoc*. 2011; 142:800–810. [PubMed: 21719802]
- Doverly M, Somogyi AA, White JM, Bochner F, Beare CH, Menelaou A, Ling W. Methadone maintenance patients are cross-tolerant to the antinociceptive effects of morphine. *Pain*. 2001; 93:155–163. [PubMed: 11427327]
- Dowell D, Haegerich TM, Chou R. CDC Guideline for prescribing opioids for chronic pain-United States, 2016. *JAMA*. 2016a; 315:1624–1645. [PubMed: 26977696]



- Dowell D, Haegerich TM, Chou R. CDC Guideline for prescribing opioids for chronic pain-United States, 2016. *MMWR Recomm Rep.* 2016b; 65:1–49.
- Dunn KM, Saunders KW, Rutter CM, Banta-Green CJ, Merrill JO, Sullivan MD, Weisner CM, Silverberg MJ, Campbell CI, Psaty BM, Von Korff M. Opioid prescriptions for chronic pain and overdose. *Ann Intern Med.* 2010; 152:85–92. [PubMed: 20083827]
- Dykstra K. Perioperative pain management in the opioid-tolerant patient with chronic pain: an evidence based practice project. *J Perianesth Nurs.* 2014; 27:385–392.
- Edlund MJ, Martin BC, Russo JE, DeVries A, Braden JB, Sullivan MD. The role of opioid prescription in incident opioid abuse and dependence among individuals with chronic noncancer pain: the role of opioid prescription. *Clin J Pain.* 2014; 30:557–564. [PubMed: 24281273]
- Eyler E. Chronic and acute pain and pain management for patients in methadone maintenance treatment. *Am J Addict.* 2012; 22:75–83.
- U.S. Food and Drug Administration (FDA). Blueprint for prescriber continuing education program. *J Pain Palliat Care Pharmacother.* 2012; 26:127–130. [PubMed: 22764849]
- U.S. Food and Drug Administration (FDA). [Accessed on May 19 2016] Standardizing and Evaluating Risk Evaluation and Mitigation Strategies (REMS). 2014. at <http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM415751.pdf>
- U.S. Food and Drug Administration (FDA). [Accessed on March 31 2016] Risk Evaluation and Mitigation Strategy (REMS) for Extended-Release and Long-Acting Opioids. 2016. at <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm>
- Fishman SM, Wilsey B, Mahajan G, Molina P. Methadone reincarnated: novel clinical applications with related concerns. *Pain Med.* 2002; 3:339–348. [PubMed: 15099239]
- Friedman JW. The prophylactic extraction of third molars: a public health hazard. *Am J Public Health.* 2007; 97:1554–1559. [PubMed: 17666691]
- Fullerton CA, Kim M, Thomas CP, Lyman DR, Montejano LB, Dougherty RH, Daniels AS, Ghose SS, Delphin-Rittmon ME. Medication-assisted treatment with methadone: assessing the evidence. *Psychiatr Serv.* 2014; 65:146–157. [PubMed: 24248468]
- Gan TJ, Habib AS, Miller TE, White W, Apfelbaum JL. Incidence, patient satisfaction, and perceptions of post-surgical pain: results from a US national survey. *Curr Med Res Opin.* 2014; 30:149–160. [PubMed: 24237004]
- Gomes T, Mamdani MM, Dhalla IA, Paterson JM, Juurlink DN. Opioid dose and drug-related mortality in patients with nonmalignant pain. *Arch Int Med.* 2011a; 171:686–691. [PubMed: 21482846]
- Gomes T, Juurlink DN, Dhalla IA, Mailis-Gagnon A, Paterson JM, Mamdani M. Trends in opioid use and dosing in the socioeconomically disadvantaged. *Open Med.* 2011b; 5:E13–E22. [PubMed: 22046214]
- Gomes T, Redelmeier DA, Juurlink DN, Dhalla IA, Camacho X, Mamdani MM. Opioid dose and risk of road trauma in Canada: a population-based study. *JAMA Intern Med.* 2013; 173:196–201. [PubMed: 23318919]
- Good, PM. The Drug Enforcement Administration and Proposed Model Guidelines for the Use of Controlled Substances in Pain Management. Federation of State Medical Boards Symposium on Pain Management and State Regulatory Policy; Dallas, Texas. 1998.
- Gordon SM, Dionne RA, Brahim J, Jabir F, Dubner R. Blockade of peripheral neuronal barrage reduces postoperative pain. *Pain.* 1997; 70:209–215. [PubMed: 9150295]
- Gordon SM, Brahim JS, Dubner R, McCullagh LM, Sang C, Dionne RA. Attenuation of pain in a randomized trial by suppression of peripheral nociceptive activity in the immediate postoperative period. *Anesth Analg.* 2010; 95:1351–1357.
- Governale, L. [Accessed November 18 2013] Outpatient Prescription Opioid Utilization in the US, Years 2000–2009. 2010. <http://www.fda.gov/downloads/AdvisoryCommitteesMeetingMaterials/Drugs/AnestheticandLifeSupportDrugsAdvisoryCommittee/ucm220950.pdf>
- Green CR, Wheeler JR, Marchant B, LaPorte F, Guerrero E. Analysis of the physician variable in pain management. *Pain Med.* 2001; 2:317–327. [PubMed: 15102236]

- Green TC, Bowman S, Davis C, Los C, McHugh K, Friedmann PD. Discrepancies in addressing overdose prevention through prescription monitoring programs. *Drug Alcohol Depend.* 2015; 153:355–358. [PubMed: 26048640]
- Griggs CA, Weiner SG, Feldman JA. Prescription drug monitoring programs: examining limitations and future approaches. *West J Emerg Med.* 2015; 16:67–70. [PubMed: 25671011]
- Gutstein, HB., Akil, H. Opioid analgesics. In: Hardman, JG, Goodman Gilman, A., Limbird, LE., editors. *The Pharmacological Basis of Therapeutics*. 10. McGraw-Hill; New York: 2001. p. 569-620.
- Haegerich TM, Paulozzi LJ, Manns BJ, Jones CM. What we know, and don't know: about the impact of state policy and systems-level interventions on prescription drug overdose. *Drug Alcohol Depend.* 2014; 145:34–47. [PubMed: 25454406]
- Haffajee RL, Jena AB, Weiner SG. Mandatory use of prescription drug monitoring programs. *JAMA.* 2015; 313:891–892. [PubMed: 25622279]
- Hargreaves, KM., Baumgartner, JC. Chapter 30: endodontic therapeutics. In: Walton, RE., Torabinejad, M., editors. *Principles and Practice Of Endodontics*. 3. Saunders; Philadelphia, PA London: 2002.
- Hersh EV, Kane WT, O'Neil MG, Kenna GA, Katz NP, Golubic S, Moore PA. Prescribing recommendations for the treatment of acute pain in dentistry. *Compend Contin Educ Den.* 2011; 22:24–30.
- Hill CS Jr. Adequate pain treatment: a challenge for medical regulatory boards. *J Fla Med Assoc.* 1996; 83:677–678. [PubMed: 9019057]
- Houtsmuller EJ, Walsh SL, Schuh KJ, Johnson RE, Stitzer ML, Bigelow GE. Dose-response analysis of opioid cross-tolerance and withdrawal suppression during LAAM maintenance. *J Pharmacol Exp Ther.* 1998; 285:387–396. [PubMed: 9580575]
- Huxtable CA, Robert LJ, Macintyres PE. Acute pain management in opioid-tolerant patients: a growing challenge. *Anesth Intensive Care.* 2011; 39:804–823.
- Hwang CS, Turner LW, Kruszewski SP, Kolodny A, Alexander GC. Prescription drug abuse: a national survey of primary care physicians. *JAMA Inter Med.* 2015; 175:302–304.
- Isaacson JH, Fleming M, Kraus M, Kahn R, Mundt M. A national survey of training in substance use disorders in residency programs. *J Stud Alcohol.* 2000; 61:912–915. [PubMed: 11188498]
- Johnson RE, Fudala PJ, Payne R. Buprenorphine: considerations for pain management. *J Pain Symptom Manage.* 2005; 29:297–326. [PubMed: 15781180]
- Jones HE, O'Grady K, Dahne J, Johnson R, Lemoine L, Milio L, Ordean A, Selby P. Management of acute postpartum pain in patients maintained on methadone or buprenorphine during pregnancy. *Am J Drug Alcohol Abuse.* 2009; 35:151–156. [PubMed: 19462298]
- Kantor TG, Cantor R, Tom E. A study of hospitalized surgical patients on methadone maintenance. *Drug Alcohol Depend.* 1980; 6:163–173. [PubMed: 6107237]
- Kaufman DW, Kelly JP, Rosenberg L, Anderson TE, Mitchell AA. Recent patterns of medication use in the ambulatory adult population of the United States: the Slone Survey. *JAMA.* 2002; 287:337–344. [PubMed: 11790213]
- Keast SL, Nesser N, Farmer K. Strategies aimed at controlling misuse and abuse of opioid prescription medications in a state Medicaid program: a policymaker's perspective. *Am J Drug Alcohol Abuse.* 2015; 41:1–6. [PubMed: 25490606]
- Kolodny A, Courtwright DT, Hwang CS, Kreiner P, Eadie JL, Clark TW, Alexander GC. The prescription opioid and heroin crisis: a public health approach to an epidemic of addiction. *Annu Rev Public Health.* 2015; 36:559–574. [PubMed: 25581144]
- Larrat EP, Marcoux RM, Vogenberg FR. Implications of recent controlled substance policy initiatives. *Health Care Law.* 2014; 39(2):126–128.
- Lewis NL, Williams JE. Acute pain management in patients receiving opioids for chronic and cancer pain. *Contin Educ Anaesth Crit Care Pain.* 2005; 5:127–129.
- Lewis M, Herndon CM, Chibnall JT. Patient aberrant drug taking behaviors in a large family medicine residency program: a retrospective review of screening practices, incidence, and predictors. *J Opioid Manage.* 2014; 10:169–175.
- Lippe PM, Brock C, David J, Crossno R, Gitlow S. The first national pain medicine summit—final summary report. *Pain Med.* 2010; 11:1447–1468. [PubMed: 21199301]

- Manchikanti L, Kaye AM, Kaye AD. Current state of opioid therapy and abuse. *Curr Pain Headache Rep.* 2016; 20:34. [PubMed: 27048483]
- Mattick R, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database Syst Rev C.* 2009:CD002209.
- Mattick R, Breen C, Kimber J, Davoli M. Buprenorphine maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database Syst Rev.* 2014:2.
- McAllister MW, Aaronson P, Spillane J, Schreiber M, Baroso G, Kraemer D, Smotherman C, Gray-Eurom K. Impact of prescription drug-monitoring program on controlled substance prescribing in the ED. *Am J Emerg Med.* 2015; 33:781–785. [PubMed: 25842283]
- Mehta V, Langford RM. Acute pain management for opioid dependent patients. *Anaesthesia.* 2006; 61:269–276. [PubMed: 16480353]
- Meyer M, Wagner K, Benvenuto A, Plante S, Howard D. Intrapartum and postpartum analgesia for women maintained on methadone during pregnancy. *Obstet Gynecol.* 2007; 110:261–266. [PubMed: 17666599]
- Meyer M, Paranya G, Keefer A, Howard D. Intrapartum and postpartum analgesia for women maintained on buprenorphine during pregnancy. *Eur J Pain.* 2010; 14:939–943. [PubMed: 20444630]
- Mezei L, Murinson BB. Johns Hopkins Pain Curriculum Development Team. Pain education in North American medical schools. *J Pain.* 2011; 12:1199–1208. [PubMed: 21945594]
- Mitra S, Sinatra RS. Perioperative management of acute pain in the opioid-dependent patient. *Anesthesiology.* 2004; 101:212–227. [PubMed: 15220793]
- Moore AP, Hersh EV. Combining ibuprofen and acetaminophen for acute pain management after third-molar extractions. *J Am Dent Assoc.* 2013; 144:898–908. [PubMed: 23904576]
- Nahin RL. Estimates of pain prevalence and severity in adults: United States, 2012. *J Pain.* 2012; 16:769–780.
- National Conference of State Legislatures. [Accessed May 19 2016] ACGME Program Requirements for Graduate Medical Education in Psychiatry, NCSL Website. 2014. at <http://www.ncsl.org/research/health/prevention-of-prescription-drug-overdose-and-abuse.aspx>
- National Opioid Use Guideline Group (NOUGG). [Accessed on May 19 2016] Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain. 2010. at <http://nationalpaincentre.mcmaster.ca/opioid/>
- Nicholson SC, Peterson J, Yektashenas B. Risk evaluation and mitigation strategies (REMS): educating the prescriber. *Drug Saf.* 2012; 35:91–104. [PubMed: 22171604]
- Nuckols TK, Anderson L, Popescu I, Diamant AL, Doyle B, DiCapua P, Chou R. Opioid prescribing: a systematic review and critical appraisal of guidelines for chronic pain. *Ann Intern Med.* 2014; 160:38–47. [PubMed: 24217469]
- O'Rourke, J. New MED Curriculum Aimed at Stemming Explosive Rise in Opioid Misuse. BU Today, Boston University Office of Marketing Communications; Boston, MA: 2016.
- Office of National Drug Control Policy (ONDCP). [Accessed on May 19 2016] National Drug Control Strategy. 2011. at from <https://www.whitehouse.gov/ondcp/2011-national-drug-control-strategy>
- Office of National Drug Control Policy (ONDCP). [Accessed on May 19 2016] National Drug Control Strategy. 2015. at <https://www.whitehouse.gov/ondcp/national-drug-control-strategy>
- PDMP Center of Excellence. Selected States. Brandeis University; Waltham, MA: 2014. Mandating PDMP Participation By Medical Providers: Current Status And Experience. at [http://www.pdmpexcellence.org/sites/all/pdfs/COE\\_briefing\\_mandates\\_2nd\\_rev.pdf](http://www.pdmpexcellence.org/sites/all/pdfs/COE_briefing_mandates_2nd_rev.pdf) [Accessed on May 19 2016]
- Pennsylvania Dental Association. [Accessed on May 13 2016] Guideline on the Use of Opioids in Dental Practice. 2015. at [https://www.padental.org/Images/OnlineDocs/ResourcesPrograms/Practice%20Management/opioid\\_dental\\_prescribing\\_guidelines3\\_13\\_15.pdf](https://www.padental.org/Images/OnlineDocs/ResourcesPrograms/Practice%20Management/opioid_dental_prescribing_guidelines3_13_15.pdf)
- Polydorou S, Gunderson EW, Levin FR. Training physicians to treat substance use disorders. *Curr Psychiatry Rep.* 2008; 10:399–404. [PubMed: 18803913]
- Reifler LM, Droz D, Bailey JE, Schnoll SH, Fant R, Dart RC, Bucher Bartelson B. Do prescription monitoring programs impact state trends in opioid abuse/misuse? *Pain Med.* 2012; 13:434–442. [PubMed: 22299725]

- Ringwalt C, Gugelmann H, Garrettson M, Dasgupta N, Chung AE, Proescholdbell SK, Skinner AC. Differential prescribing of opioid analgesics according to physician specialty for Medicaid patients with chronic noncancer pain diagnoses. *Pain Res Manage*. 2014; 19:179–185.
- Rodriguez-Monguio R, Spielberger K, Seoane-Vazquez E. Examination of risk evaluation and mitigation strategies and drug safety in the US. *Res Social Adm Pharm*. 2014; 10:232–238. [PubMed: 23611865]
- Rutkow L, Chang HY, Daubresse M, Webster DW, Stuart EA, Alexander GC. Effect of Florida's Prescription Drug Monitoring Program and pill mill laws on opioid prescribing and use. *JAMA Int Med*. 2015; 175:1642–1649.
- Schnitzer TJ, Ferraro A, Hunsche E, Diprerpol Kong SX. A comprehensive review of clinical trials on the efficacy and safety of drugs for the treatment of low back pain. *J Pain Sympt Manage*. 2004; 28:72–95.
- Scholten W, Henningfield JE. Negative outcomes of unbalanced opioid policy supported by clinicians, politicians, and the media. *J Pain Palliat Care Pharmacother*. 2016; 30:4–12. [PubMed: 26890500]
- Shah S, Kapoor S, Durkin B. Analgesic management of acute pain in the opioid tolerant patient. *Curr Opin Anesth*. 2015; 28:398–402.
- Shoemaker S, Posniak A, Subramanian R, Mauch D. Effect of six managed care pharmacy tools: a review of the literature. *J Manage Care Pharm*. 2010; 16(6 Suppl):S3–S20.
- Stanos S. Evolution of opioid risk management and review of the classwide REMS for extended-release/long-acting opioids. *Phys Sportsmed*. 2012; 40:12–20.
- Starrels JL, Becker WC, Alford DP, Kapoor A, Williams AR, Turner BJ. Systematic review: treatment agreements and urine drug testing to reduce opioid misuse in patients with chronic pain. *Ann Intern Med*. 2010; 152:712–720. [PubMed: 20513829]
- Stayner RS, Copenhaver DJ. Opioids, pain management and the law. *Curr Opin Anaesthesiol*. 2012; 25:566–571. [PubMed: 22914352]
- Surratt HL, O'Grady C, Kurtz SP, Stivers Y, Cicero TJ, Dart RC, Chen M. Reductions in prescription opioid diversion following recent legislative interventions in Florida. *Pharmacoepidemiol Drug Saf*. 2014; 23:314–320. [PubMed: 24677496]
- Thomas CP, Kim M, Nikitin RV, Kreiner P, Clark TW, Carrow GM. Prescriber response to unsolicited prescription drug monitoring program reports in Massachusetts. *Pharmacoepidemiol Drug Saf*. 2014; 23:950–957. [PubMed: 24920376]
- Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, Villiger P, Egger M, Juni P. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. *BMJ*. 2011 (epub ahead of print).
- Urquhart DM, Hoving JL, Assendelft WJJ, Roland M, van Tulder MW. Antidepressants for non-specific low back pain. *Cochrane Database of System Rev C*. 2008:CD001703.
- Vadivelu N, Kai AM, Kodumundi V, Berger JM. Challenges of pain control and the role of the ambulatory pain specialists in the outpatient surgery setting. *J Pain Res*. 2016; 9:425–435. [PubMed: 27382329]
- Volkow, ND. [Accessed on May 19 2016] America's Addiction to Opioids: Heroin and Prescription Drug Abuse. 2016. at <https://www.drugabuse.gov/about-nida/legislative-activities/testimony-to-congress/2016/americas-addiction-to-opioids-heroin-prescription-drug-abuse>
- Walsh SL, Eissenberg T. The clinical pharmacology of buprenorphine: extrapolating from the laboratory to the clinic. *Drug Alcohol Depend*. 2003; 70:S13–S27.
- Webster LR. Pills, policies, and predicaments: the unintended consequences of a health care system's policy toward opioids. *Pain Med*. 2013; 14:1439–1440. [PubMed: 24588851]
- White JM. Pleasure into pain: the consequences of long-term opioid use. *Addict Behav*. 2004; 29:1311–1324. [PubMed: 15345267]
- Wolfred MZ, Gilson AM, June DL, Cleary JF. Opioid analgesia for pain control: Wisconsin physicians' knowledge, beliefs, attitudes, and prescribing practices. *Pain Med*. 2009; 11:425–434. [PubMed: 20002590]
- Woodcock J. A difficult balance-pain management, drug safety, and the FDA. *N Engl J Med*. 2009; 361:2105–2107. [PubMed: 19940297]