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Clinical Practice Guidelines for Pain Management in Acute Musculoskeletal Injury

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BACKGROUND

Drug overdose deaths have become an epidemic in the United States. In the past fifteen years, deaths related to drug overdoses in the United States have tripled, mostly due to the rise in opioid-related deaths.[1, 2] In the same time period, almost half a million people have died from prescription drug overdoses.[1, 2] Opioids, including prescription drugs and heroin, are involved in 61% of drug overdose deaths.[22] The rate of increase in deaths from commonly prescribed opioids has slowed slightly in the past few years, while death rates from the synthetic opioids fentanyl and heroin have increased by 72% and 21%, respectively.[22] This epidemic has taken a significant toll on the health of the nation, with emerging findings that opioid-related deaths have led to a 0.21 year reduction in average life expectancy – contributing to the overall decrease in life expectancy from 2014 to 2015.[3]

The increase in opioid overdose deaths aligns with a proportional increase in opioid prescribing rates. Opioid prescriptions increased substantially from 2006 until 2012[4] with a desired focus on treating patient pain. Family medicine physicians overall provide the most opioids of any specialty; however, orthopaedic surgeons prescribe 7.7% of prescriptions despite representing only 2.5% of physicians.[5] The increase in opioid prescriptions was unfortunately not associated with the anticipated reduction of reported pain among Americans.[6] Without an improvement in patient outcomes, these prescriptions are needlessly associated with a high risk of abuse. Adding to the problem of oversupply for needs, many opioids go unused following orthopedic surgery[7, 8] creating the possibility of nonmedical usage or diversion. Furthermore, of the patients who receive a first opioid prescription of any duration, 21% progress to receiving more prescriptions episodically and 6% progress to long-term use.[9] Up to half of patients who

take opioids for at least three months remain on opioids five years later and are likely to become life-long users.[10-12] Therefore, changing prescribing habits has been a high priority.

Due to the increasing recognition of the opioid crisis, several professional societies, healthcare systems, pharmacies, insurance companies, and governmental organizations have released guidelines and toolkits for the safe prescribing of opioids. While some of these guidelines address certain aspects of pain from musculoskeletal conditions, many are focused on the management of chronic pain, and unfortunately few give concrete examples of practical methods and prescribing practices that can be easily implemented when caring for acute musculoskeletal injuries. Thus, we aimed to produce comprehensive guidelines and recommendations that can be utilized by orthopaedic practices as well as other specialties to improve the management of acute pain following musculoskeletal injury.

METHODS

Panel and Target Audience

This guideline aims to provide evidence-based recommendations for the management of acute musculoskeletal pain. A panel of 15 members with expertise in orthopaedic trauma, pain management, or both was convened to review the literature and develop recommendations on acute musculoskeletal pain management. Chronic pain is outside the scope of this guideline.

Literature Review

The panel met in person in October 2017 to define the scope of the guideline and identify important topics for inclusion. These topics included: cognitive strategies, physical modalities, opioid safety and effectiveness, multimodal pharmaceutical strategies, medical assistance therapy, nonsteroidal anti-inflammatory drugs and fracture healing, nerve/regional/field blocks, pain and sedation assessment strategies, and healthcare system strategies. One or two panel

members were assigned to draft recommendations for each topic area. Literature searches were conducted through September 2018. Information about each included article is available in the Supplementary Digital Content table,http://links.lww.com/JOT/A648.

Grading Process

The methods described by the Grading of Recommendations Assessment, Development, and Evaluation Working Group were applied to each recommendation.[13] This method yields a grade for the strength of the recommendation and a grade for the quality of the evidence. The grading of the evidence was based on the study designs, number of studies, sample sizes, and consistency of results among different studies. The panel assigned recommendations as "strong" (practices in which benefits are sure to outweigh potential harms) or "conditional" (the evidence was weaker or if the benefits do not significantly outweigh potential harms).

Approval of Guideline

Recommendations from each topic area were combined to produce a comprehensive guideline for management of acute musculoskeletal pain. All panel members reviewed and revised the combined guideline. The guideline was submitted to the Orthopaedic Trauma Association (OTA) for review and was approved on October 16, 2018.

Best Practice and Pain Management Recommendations

Due to the increasing recognition of the opioid crisis, several professional societies, healthcare systems, pharmacies, insurance companies, and governmental organizations have released guidelines and toolkits for the safe prescribing of opioids.[14-39] While some of these guidelines address certain aspects of pain from musculoskeletal conditions, many are focused on the management of chronic pain, and few give concrete examples of practical methods and

prescribing practices that can be easily implemented when caring for acute musculoskeletal injuries.

We provide the attached Best Practice Recommendations and Pain Medication Recommendations (Tables 1-4) with the hope that they can be utilized by orthopaedic practices as well as other specialties (e.g. primary care, emergency medicine) to improve the management of acute pain following musculoskeletal injury. The Best Practice Recommendations for acute pain management following musculoskeletal injury are supplemented with the corresponding in-depth reviews presented in this full document. The Pain Medication Recommendations are divided into 3 clinical scenarios - Major Musculoskeletal Injury Procedure (e.g. operative fixation of long bone or complex joint fracture, extensive soft tissue injury or surgery, etc.); Minor Musculoskeletal Injury Procedure (e.g. operative fixation of small bone or simple joint fracture, minimal soft tissue dissection or surgery, etc.); Non-operative Musculoskeletal Injury (e.g. closed management of injury, laceration repair, etc.). The Best Practice Recommendations and the Pain Management Recommendations are meant to be used in conjunction with each other and should be individualized per treating physician discretion according to patient characteristics, local practice preferences, and applicable state laws.

Insert Tables 1, 2, 3, and 4 near here

RECOMMENDATIONS

Cognitive and Emotional Strategies

- The panel recommends discussing alleviation of pain, expected recovery course, and patient experience at all encounters (strong recommendation, moderate quality evidence).
- The panel recommends connecting patients with pain that is greater or more persistent than expected and patients with substantial symptoms of depression, anxiety, or post-traumatic stress or less effective coping strategies (greater catastrophic thinking, lower self-efficacy) to psychosocial interventions and resources (strong recommendation, low quality evidence).
- The panel recommends that clinicians consider using anxiety reducing strategies to increase self-efficacy and promote peace of mind with patients like aromatherapy, music therapy, or cognitive behavioral therapy (strong recommendation, low quality evidence).

Nociception and Pain

Nociception is the physiology of actual or potential tissue damage. Pain is the unpleasant thoughts, emotions, and behaviors that accompany nociception. There is wide variation in pain intensity for a given nociception.[40] Pain catastrophizing is an ineffective coping strategy characterized by unhelpful preparation for the worst including rumination and helplessness.[41] Greater catastrophic thinking is consistently associated with greater pain intensity.[42] Increased symptoms of anxiety and depression, and greater alcohol use are also associated with higher pain intensity, while self-efficacy and fewer symptoms of depression are associated with less pain.[43-45]

Studies of musculoskeletal injuries, including ankle sprains and fractures, have found no association between pain intensity and degree of nociception (injury severity). Variations in pain intensity and magnitude of limitations are accounted for more by measures of psychosocial aspects of illness than by measures of pathophysiology.[44, 46-53]

There are also cultural differences in pain intensity and alleviation of pain with medication. Studies document good pain relief using non-opioid medication in patients recovering from fracture surgery in The Netherlands and Vietnam.[54-57] In the United States, however, patients that take more opioids in the hospital after fracture surgery have more pain and less satisfaction with alleviation of pain.[43-45] These findings suggest that psychological factors play a significant role in the intensity of pain for a given nociception.

Persistent pain in the absence of infection or implant problems correlates with psychosocial factors.[53, 56, 58-77] Pain intensity, magnitude of limitations, and continued opioid use are associated with greater symptoms of depression or post-traumatic stress disorder and less effective coping strategies (e.g. greater catastrophic thinking).

Chronic pain is defined as pain lasting beyond the usual course of healing or more than 3 to 6 months, which affects the individual's daily functioning and well-being.[78] Several non-modifiable risk factors have been identified for the development of chronic pain including female gender, age greater than 65 years, intense acute pain, and low socioeconomic status. Several modifiable risk factors have also been identified including greater pain catastrophizing, greater pain-related fear, and greater symptoms of anxiety, depression, and post-traumatic stress disorder. Identifying and addressing psychosocial factors may limit persistent pain.

Psychosocial Interventions

A notable portion of trauma patients have substantial symptoms of anxiety, depression, and PTSD months after injury. Giving opioids for pain that is more intense and disabling than expected might represent a misdiagnosis and mistreatment of stress, distress, and less effective coping strategies.

Initial studies of psychosocial interventions to limit psychological distress and improve comfort and ability have had mixed results.[62, 79-94] The goals of these interventions are to improve overall mental health, decrease rates and severity of depression, anxiety and post-traumatic stress disorder. Interventions studied include cognitive-behavior therapy, self-management interventions and training, educational information access, peer support, and online social networking. Cognitive behavioral interventions have positive effects on pain relief in some trials.[58, 95, 96] There is also evidence that web-based CBT is effective.[97-99] Meta-analyses of Music Therapy demonstrates decreased anxiety and better sleep in the setting of chronic medical illness.[100] Music Therapy has also demonstrated positive effects on pain relief and opioid dose reduction. Similarly, systematic reviews of aromatherapy have demonstrated anxiolytic effects [101]and pain reduction.[102] Further research on the utility of various interventions can help elucidate the most effective resources for trauma patients.

Physical Strategies

TENS

- The panel recommends the use of transcutaneous electrical stimulation (TENS) as an adjunct to other immediate post-injury or postoperative pain treatments (strong recommendation, low quality evidence).

- The panel can neither recommend nor discourage a specific TENS device or protocol. Regimens that incorporate suboptimal frequencies not approaching a "sub-noxious or maximal tolerable/painful" setting lack effective pain modulation and should be avoided (conditional recommendation, low quality evidence).

Transcutaneous electrical nerve stimulation (TENS) attempts to modulate pain through delivery of low-voltage electric currents over the skin from a small portable device. The stimulation of large diameter peripheral afferent nerve fibers is believed to reduce pain by activating opioid receptors through an endogenous descending inhibitory pathway.[103] The contraindications to the use of TENS include the presence of a pacemaker or implanted defibrillator, broken skin at the site of application, or significant lymphedema.

There are mixed results on the adjunctive use of TENS to modulate pain largely due to a relative paucity of high quality trials and significant interstudy heterogeneity due to the lack of any specific standardized treatment protocols. The panel's literature review was restricted to TENS studies within the last 20 years.

The American Pain Society's 2016 Clinical Practice Guideline for the management of postoperative pain recommends the consideration of TENS as an adjunctive modality with treatments directed near the surgical wound. The review panel found insufficient evidence for specific TENS regimens, but emphasized that positive effects were stronger when optimal predefined stimulation parameters were utilized.[103]

A meta-analysis (21 randomized clinical trials, RCTs) of TENS as an adjunct to reduce postoperative analgesic consumption found that the effectiveness may depend upon the current amplitude. The authors only included studies that report a "strong and/or definite sub-noxious, and/or maximal non-painful, and/or maximal tolerable" stimulation with currents >15mA or a

pulse frequency of 1-8Hz (acupuncture-like TENS; ALTENS) or 25-150Hz (TENS). The review found TENS (vs placebo TENS) around the surgical wound significantly reduced postoperative analgesic consumption by 26.5 % (range -6 to 51%): sub-noxious stimulation reduced opioid consumption by 35.5% whereas nonspecific trials yielded less effect (4.1% reduction). Overall difference in analgesic consumption favored TENS versus placebo with optimal median frequencies at 2Hz for ALTENS or 85Hz for TENS.[104]

The effectiveness of TENS within the orthopaedic literature is limited by non-standardized clinical trials often without reported or consistent TENS treatment protocols. Adjunctive TENS use within the immediate postoperative period after a total knee arthroplasty (TKA) postulates a trend towards favorable mean weighted reduction in opioid consumption versus placebo-TENS or standard care (3 Meta-analysis and 1 RTC).[105] One systematic review and meta-analysis found TENS decreased pain severity at 1,2 and 6 months after TKA, but this was based on low quality studies.[105] Interestingly, both TENS and placebo-TENS (45-sec cutoff) were found to decrease postoperative TKA pain with active extension and fast walking highlighting a potential placebo effect that subsided by 6 weeks postoperatively vs. standard treatment.[106] A prospective double-blind randomized trial on arthroscopic rotator cuff repair found TENS to significantly reduce immediate post-op opioid use by 25% at both 48hrs and 1 week.[107] These results are moderately consistent with non-orthopaedic literature where TENS decreased postoperative opioid analgesic requirements (by 53% with mixed frequencies vs 35% with high frequency and 32% with low frequency settings) as well as opioid-related side effects when utilized as an adjunct to patient-controlled analgesia after lower abdominal OB/GYN surgery.[108] In contrast, while TENS was determined useful after thoracic surgical procedures (only when less invasive approaches yield

mild to moderate post-op pain), TENS was ineffective for severe pain with invasive approaches.[109]

A meta-analysis (27 RCTs) of six different types of electrical stimulation determined that interferential current (IFC), a less common modality, was the only treatment to effectively modulate pain intensity and change pain VAS scores (standardized mean difference=2.06, 95% CI: 1.1-3.19), that the effect of high frequency TENS was uncertain and that low frequency TENS was not effective.[110]

In conclusion, our systematic review indicates that TENS, when applied using strong, sub-painful frequencies, is an effective multimodal adjunct to modulate acute orthopaedic injury and postoperative pain. Recent publications demonstrate a substantial degree of inter-study heterogeneity, most notably inconsistent descriptions of both TENS dosing intensities and standardized outcome measures. The long-term tolerance of same dose TENS parameters and strategies to prolong its effect is largely unknown. Higher quality clinical trials are necessary to provide stronger evidence in favor of TENS as a consistent treatment for acute pain and perioperative pain modulation.

Cryotherapy

- The panel recommends the use of cryotherapy for acute musculoskeletal injury and the post-surgical orthopaedic patient as an adjunct to other postoperative pain treatments (conditional recommendation, low quality evidence)
- The panel cannot recommend a specific cryotherapy delivery modality or protocol (no recommendation, limited evidence)

Cryotherapy is the application of an external cold source in which the desired effect is a drop in tissue temperature. Cold sources that have historically been used include ice bags, cold gel packs, ice massage, cold water submersion, gaseous cryotherapy, and continuous-flow cryotherapy devices with and without pneumatic compression. Basic science studies have shown that the biologic effects of cold therapies are multifactorial. A decrease in tissue temperature results in decreased tissue edema and microvascular permeability,[111, 112] reduced delivery of inflammatory mediators,[112-116] reduced blood flow via vasoconstriction,[116-120] overall net decrease in tissue metabolic demand, and subsequent hypoxic injury.[116-118, 120] Additionally, the decrease in tissue temperature has been shown to increase the threshold of painful stimuli and increase the tolerance to pain.[121]

Multiple studies have looked at the efficacy of cryotherapy in the post-operative orthopaedic patient for various anatomic areas including the knee, hip, shoulder, foot and ankle, wrist, and hand. Among the studies that evaluated cryotherapy versus a non-cryotherapy control, 10 randomized controlled trials and two meta-analyses have shown a significant benefit for pain control.[105, 122-132] Contrary to this, there have been eight randomized controlled trials that have shown no benefit to cryotherapy compared to a non-cryotherapy control.[133-140] Many studies have also looked at cryotherapy's ability to decrease opioid consumption compared to a non-cryotherapy control. Of these studies, eleven have shown a significant decrease in pain medication consumption[105, 123, 125-127, 129, 131-133, 138, 141] compared with five studies showing no difference.[134-136, 139, 140]

Many randomized controlled trials have compared continuous-flow cryotherapy devices to ice bags or packs. Nine studies have failed to show a difference in pain scores[142-150] whereas five studies have shown improved pain with continuous-flow cryotherapy.[151-155] No studies have shown superior pain control with ice bags or packs compared to continuous cryotherapy.

There are also inconclusive results pertaining to the difference in pain medication consumption when comparing continuous-flow cryotherapy with ice bags or packs. Five studies have demonstrated a decreased need for opioids with continuous cryotherapy,[148, 150, 151, 154, 156] one study showed a lower consumption of pain medication with the use of ice packs,[157] and five RCTs failed to show a difference between these two cryotherapy modalities.[142, 145, 147, 149, 158] It is possible that continuous-flow cryotherapy results in a higher patient satisfaction with the cryotherapy treatments[142, 148, 150] and that there may also be a benefit to continuous-flow cryotherapy at night.[159] It is important to note the methodologic variability within the cryotherapy literature. Variables such as cryotherapy source, temperature, duration, and frequency can vary drastically from treatment groups in the same study, as well as study to study, making the assessment on the magnitude of effect difficult to determine. Because of the current literature's methodological heterogeneity, we are unable to favor one method of cryotherapy application, protocol, or both.

Like most therapeutic interventions, cryotherapy can result in complications. Nerve palsies have been reported in the literature, mostly involving more superficial nerves such as the peroneal nerve, lateral femoral cutaneous nerve, ulnar nerve, and supraclavicular nerve. Care must be taken to provide sufficient insulation between the skin and the cryotherapy source, especially in patients with minimal subcutaneous fat. Nerve injuries can range from brief

paresthesias to complete axonotmesis.[160, 161] Frostbite has also been a concern, but to our knowledge has not been reported as a result of cryotherapy after an orthopaedic procedure.

Overall, the body of literature provides preliminary support for use of cryotherapy for acute pain management. However, future studies should focus on determining the most efficacious method of application and protocol for cryotherapy.

Opioid Safety and Effectiveness

- The panel endorses that all opioids used for pain carry a risk for misuse. Opioids are also associated with adverse clinical events. Patient comfort and safety must be carefully balanced when prescribing opioids. Due to the potential for misuse of all opioids, the panel recommends that the prescriber should utilize the lowest effective dose for the shortest period possible (strong recommendation, high quality evidence).
- The panel recommends not prescribing benzodiazepines in conjunction with opioids due to the significant risks of inconsistent sedation and potential for misuse (strong recommendation, high quality evidence).
- The panel recommends avoiding long-acting opioids in the acute setting (strong recommendation, moderate quality evidence).
- The panel recommends prescribing precisely. Commonly written prescriptions with ranges of dose and duration can allow tripling of daily dose to levels consistent with adverse events (strong recommendation, low quality evidence).

Opioids are the most commonly used medications for treatment of the majority of severe pain conditions.[162] All opioids come with some level of safety concern. Regardless of the formulation used, there is always a risk of adverse events, as well as abuse, addiction or both. The number and severity of adverse events from opioids is related to their potency, half-life, and mode of use.

The number of milligrams in the dosage is not an indication of how strong the medication might be. Potent opioids (e.g., fentanyl is 50-100 times as potent as morphine) increase the number and severity of events. Although oxymorphone and oxycodone are about equally effective in treating pain, more adverse events are seen with oxymorphone due to its higher potency.[163] Oxymorphone has 3-7 times the efficacy of morphine while oxycodone is only 1.5 times greater. Currently, immediate release opioids are prescribed at a significantly higher rate than extended release options.[164] These extended release medications result in a 4.6 fold higher abuse rate and a 6.1 times increased diversion potential.[164] The risk of addiction and abuse also has a strong correlation with the length of time the opioids are prescribed. While some patients may become addicted after long term therapy, a significantly larger proportion will show behavior of medication misuse and illicit drug use.[165]

The main formulations on the market have vastly different pharmacokinetics. Immediate release opioids, which cause serum opioid levels to rapidly rise and decline with a shorter half-life, have a shorter period of pain relief. Long-acting ('continued-release' tablets) may deliver opioids for a longer period, but the amount of opioid absorbed is less per unit of time. This results in less fluctuation in serum drug levels keeping opioid concentration in the therapeutic range.[166] For the inpatient setting, long-acting opioids may have the same effectiveness as short-acting opioids when used as monotherapy, but given newer multimodal pain management regimens this is not recommended current practice.[167] Both short-acting and long-acting opioids have been shown to be effective in treating pain and increasing quality of sleep with the main difference being the number of pills prescribed will be higher in the short-acting group.[168-170] Other drug formulations have been created to include supposed abuse deterrent properties, but in actuality may have a similar profile in regards to effectiveness and adverse events.[171] Combining

opioids with other drugs has been shown to be more effective in managing pain than opioids alone. More specifically, combining opioids with NSAIDs has been shown to be more effective than opioids alone.[172] Benzodiazepines do not have this beneficial synergy. Taking any of these formulations with food does not change the maximum dose of the medication delivered although when taken after a high fat meal, the time to maximum concentration is delayed.[173]

The literature comparing the difference of the safety and efficacy of opiates for the treatment of pain in acutely injured musculoskeletal patients is scarce. The majority of the literature on safety and efficacy of opioids is in regard to chronic pain from both malignant and non-malignant conditions. The evidence in these areas is not strong.[162] There is very little in the literature discussing safety and efficacy in the short-term post-injury setting. Hence, the appropriate dose for specific injuries or conditions is not well defined. Standard prescribing habits appear to routinely provide an excess amount of medication. A recent study found 81% of patients took 20 or fewer pills after knee arthroscopy.[174] A study of opioid use by 250 patients who had undergone elective outpatient upper extremity surgery showed that while all patients were prescribed opioids for 30 days (30 pills), 52% used their prescription for pain control for only two days or less. On average, each patient took 11 pills leaving 19 pills unused. With fewer pills prescribed, there was a 79% reduction of leftover pills in the community, thus decreasing the potential for diversion.[175]

Leaders in musculoskeletal care need to develop specific strategies based on burden of disease. Other nonopioid medications should be used with an intent to obtain balanced patient comfort and safety. Some data has shown that the risk for dependency increases significantly with increasing duration of use.[176] Every effort should be made to minimize prescription length.

The main cause of death in patients using opioids is respiratory depression. This can occur with any opioid regardless of the type or formulation. This deadly complication is dose and concentration dependent with many other variables like opioid tolerance, BMI, respiratory disease, obstructive sleep apnea, and concomitant medications. Patients with a history of opioid use are expected to require more opioids for adequate pain relief while experiencing fewer adverse events due to tolerance.[166, 177] Common non-life threatening side effects seen in approximately 10% of patients prescribed immediate release opioids are pruritus, nausea, vomiting, dizziness, headache and somnolence.[178, 179] Addiction and abuse are complications often seen by psychiatrists or psychologists. Despite early, unsubstantiated claims of improved safety with long-acting opioids,[180] the relative abuse and addiction potential with short-acting or long-acting opioids remains a question. Some evidence suggests that there is no difference in illicit drug use, misuse, or both when comparing long-acting vs short-acting opioids suggesting that prescribing long-acting opioids will not reduce abuse potential.[181] A contradictory study showed less drug-seeking behavior with extended release formulations.[182] Benzodiazepines should not be prescribed in conjunction with opioids because the risk of overdose and death increases significantly. There is a 3.9 times risk of overdose due to respiratory depression when opioids and benzodiazepines are prescribed at the same time.[183]

Combination Pharmaceutical Strategies

Multimodal Analgesia

- The panel recommends the use of multimodal analgesia (MMA) as opposed to opioid monotherapy for pain control (strong recommendation, moderate quality evidence).

- The panel recommends the use of periarticular injections as an adjunct to pain management that improves pain control post-operatively (strong recommendation, moderate quality evidence).
- The panel cannot recommend specific multimodal analgesia regimens at this time without further scientific evidence. MMA should be tailored to patients' injuries and medical co-morbidities (strong recommendation, very low quality evidence).

Multimodal analgesia (MMA), also referred to as balanced analgesia, is the use of multiple analgesic medications (opioid and non-opioid) and non-pharmacologic interventions designed to affect peripheral and or central nervous system loci in the pain pathway.[103] Benefits of this treatment paradigm include potentiation of multiple medication effects and greater pain control without relying on any one class of medication. MMA therefore mitigates the risk profile of each medication, while allowing for synergistic pain control from different classes of medication. Successful post-operative MMA may include psychotherapy, physical therapy, non-steroidal anti-inflammatories (NSAIDs), acetaminophen, gabapentinoids, regional anesthesia (single shot or peripheral nerve catheters), local injections, and opioids. Recent reviews,[184] meta-analyses,[185] and RCTs[186] have shown that multimodal analgesia is effective in the perioperative period. There is, however, a paucity of literature in the orthopaedic trauma population, and therefore literature from other sub-specialties and surgical fields was included.

The majority of the orthopaedic literature addresses the arthroplasty population (14 articles). These articles addressed the following three main clinical trial questions: (1) comparison of different periarticular injections, (2) oral or "standard" medication regimen versus

addition of a peripheral nerve block (covered in later section), and (3) oral or "standard" medication regimen versus MMA.

Four studies compared "standard" medication regimens versus MMA. For example, additions to MMA strategies include gabapentin[187] and duloxetine.[188] Gabapentin seemed to decrease pain scores, but not opioid consumption,[187] while duloxetine decreased opioid consumption, but not pain scores.[189]

Finally, two studies evaluated the cost-effectiveness of MMA in arthroplasty patients. In both cases, the use of multimodal therapy decreased hospital costs, directly related to medication, as well as overall hospital costs for patient stay.[190, 191]

There is limited literature regarding the use of MMA in other non-trauma orthopaedic subspecialties. Two articles evaluated the use of MMA in foot and ankle surgery where MMA decreased length of stay[192] and decreased pain in the first 24 hours after surgery.[193] In spine surgery, the addition of MMA to a standard PCA regimen, decreased opioid use and improved mobilization.[194] When compared with intravenous medication only, MMA decreased VAS at all time points following lumbar fusion surgery.[195]

In orthopaedic trauma, addition of periarticular injection to standard pain control for hip hemiarthroplasty improved VAS and reduced opioid usage early in the postoperative course.[196] Surgical site injection also improved pain for femoral fracture patients.[197] In the upper extremity, MMA compared with PCA showed additional need for pain rescue in the PCA group and lower patient satisfaction.[198] In a study of emergency department fracture patients. Intravenous (IV) morphine or IV Tylenol + oral oxycodone was equally effective for pain control in the first hour after administration. However, patients in the IV morphine group did have less nausea and site itching.[199]

The use of corticosteroids for postoperative pain has been validated in the literature in other specialties in medicine. As with other medications there are risks associated with the use of corticosteroids. Systemic side effects often associated with long-term therapy include the following: Cushingoid appearance, hirsutism, exophthalmos, hypertension, arrhythmias, gastritis, osteoporosis, avascular necrosis, dysphoria and hypokalemia just to name a few. From a postoperative perspective, concerns include a decrease or delay in wound healing potential and infection. There are no data to indicate that short-term use of corticosteroids causes an increase in infection. It is not recommended to use corticosteroids in patients over the age of 60 and in immunocompromised patients as some data suggests there is an increase in healing time.[200] An increase in blood glucose 24 hours post-surgery should be expected and has not been associated with an increase in the rate of infection.[201]

Corticosteroids given orally or intravenously can decrease the use of opioid analgesics by 50%.[202] Benefits of corticosteroids include a decrease in postoperative nausea, decrease in opioid requirements, decrease in the length of hospital stay and more complete pain relief.[203], [204] The smallest dose that is effective should be prescribed. Doses ranging from 15mg of dexamethasone to 0.1mg/kg have been shown to be effective with no complications.[201, 203, 205-207] A meta-analysis of perioperative use corticosteroids concludes an "Intermediate dose dexamethasone (0.11 to 0.2 mg/kg) is a safe and effective multimodal pain strategy after surgical procedures. The preoperative administration of the drug provides a greater effect on postoperative pain."[201] Physicians should consider perioperative dosing of corticosteroids in low risk patients and especially in patients at risk for dependency.

Managing Acute Pain for Patients on Long Term Opioids at Presentation

The panel recommends that perioperative analgesia should be managed with a multimodal analgesia regimen in all opioid-tolerant patients (Strong recommendation, moderate quality evidence).

- The panel recommends coordinating with acute pain service (APS) (or addiction medicine or psychiatry depending on resources) when inpatient and the patient's prescriber when outpatient to ensure that there is only one prescriber for patients on medication assisted therapy (methadone, buprenorphine, or naltrexone), patients using illicit opioids, or patients misusing prescription opioids (Strong recommendation, moderate quality evidence).

Opioid-tolerant patients present a clinical challenge to effective perioperative pain management. These patients have a medical condition and should be treated with the same respect and dignity as a patient with any other pre-surgical medical condition. Developed nations have observed a large increase in the number of opioid-tolerant patients over the last decade.[103, 208] In the United States, a combination of expanding heroin abuse, pain control metrics, and pharmacologic development of long-acting opioids has resulted in a dramatic rise in the number of opioid-tolerant patients. Managing perioperative pain in the opioid-tolerant patient is both a medical and a social challenge. Opioid-tolerant patients are at increased risk of receiving inadequate perioperative analgesia.[103] This risk exists as the result of (a) a social stigmatization of opioid prescription and consumption[209]; (b) concerns for drug-seeking behavior [210] or relapse of recovering addicts, or both; and (c) an incomplete understanding of opioid agonist and opioid replacement therapy pharmacokinetics.[211]

Opioid-tolerant patients present with one of the following three clinical scenarios: (1) scheduled, prescribed opioid (short-acting or long-acting) regimens; (2) prescribed medical assist therapy (methadone, buprenorphine); (3) illegal consumption of prescription or non-prescription opioids.[212] Each patient can be further subdivided into those who are actively experiencing acute pain in an emergent setting (secondary to trauma) or whose treatment necessitates elective surgery (nonunion, mal-union, infection, hardware removal). The care of these patients can be difficult and there is little literature to guide treatment.

At the time of this publication, there are a limited number of observational studies examining acute perioperative pain management in the opioid-tolerant patient. However, care must be taken when managing these patients. In two studies on orthopaedic trauma populations, it has been shown that patients on opioids are at higher risk for receiving prescriptions from multiple prescribers in the postoperative period, which leads to more prescriptions, higher doses and longer duration of opioid use.[213, 214] What follows is a review of available literature and clinical recommendations for perioperative analgesia in the opioid-tolerant patient.

It is critical to identify opioid users immediately after injury or in the pre-operative period to avoid uncontrolled acute pain. Physicians should obtain information on type, dose, frequency, and last consumption of all opioids, which will allow conversion to morphine equivalent doses. The opioid-tolerant patient experiences pain, physiologically, differently than the opioid-naive patient[103, 211, 215-217] because of:

a. Cross tolerance occurs between different opioids
b. Increased sensitivity to natural and experimental pain.[103, 211, 218, 219]
    i. Results in higher than expected post-operative pain scores and slower resolution of acute pain in the postoperative period.[211, 218]

c. High affinity partial μ-agonist and antagonist block the effect of standard opioids. When these medications are utilized patients require high opioid doses to displace competitive medications, before analgesia takes effect.

The following sections provide brief recommendations for specific populations of opioid-tolerant patients, including those taking chronic short-acting opioid therapy, those using illicit opioids, and those taking methadone, buprenorphine or naltrexone.

Chronic short-acting opioid therapy

Perioperative pain management of patients consuming routine and scheduled oral opioids should include:

1. Instructions to continue baseline medication the morning of surgery through the post-operative period.[220]
    a. If transdermal fentanyl patches are used pre-operatively, patients should be converted to an IV morphine equivalent dose. This is because of alterations in fentanyl release during fluid shifts and body temperature changes observed with surgery.[220, 221]
2. Titrate short-acting μ-agonist to effective pain control
3. When oral medications cannot be consumed the 24 hour morphine equivalent dose should be calculated for conversion to intra-venous management until oral medications can be reinstituted.[215]

Illicit Opioids

Perioperative pain management is further complicated by inaccurate consumption history, and variation in strength of illicit drugs:

1. If available, consult addiction medicine, acute pain service, or psychiatry.[103]

Methadone *(Slow release oral morphine or opioid agonist).*[215]

Perioperative pain management of patients consuming methadone should include:

1. If available, consult addiction medicine, acute pain service, or psychiatry.[103]
2. Continue baseline methadone throughout the perioperative period including the morning of surgery
3. If unable to take oral medication, convert 24-hour dose to IV methadone according to conversion chart and administer in 2-4 divided doses.
    a. Pharmacokinetics of methadone are influenced by CYP450 and CYP3A4 metabolism and may also vary based upon patient's own metabolism. Consult pharmacist or acute pain service specialist for conversion to the appropriate morphine equivalent dose.[222]
4. Supplement perioperative pain with short-acting agonist
5. Close respiratory monitoring due to combined effects
6. Educate patient on acute opioid taper

Buprenorphine *(partial μ-agonist alone or mixed with kappa antagonist (naloxone)).*[215, 223-225]

Addiction medicine, acute pain service, or psychiatry (depending on local resources and expertise) should be consulted when managing patients on buprenorphine, which is commonly administered transdermally for chronic pain and sublingually for substitution in opioid abusers. Owing to the medication high affinity for Mu receptors and kappa antagonist effect other agonists may have limited analgesia effect and typically require high doses to achieve affect. For this reason, close respiratory monitoring is required when using short and long-acting opioids. Perioperative pain management of patients consuming buprenorphine will vary according to the clinical setting:

1. Elective surgery
    a. Mild to moderate pain
        i. Consider management with increased doses of buprenorphine (when low doses are prescribed at baseline)
        ii. Continue buprenorphine and add short-acting μ-agonist
    b. Moderate to severe pain
        i. Discontinue 72-hours prior to surgery and convert to short-acting agonist.
            1. Higher than expected doses are anticipated for analgesia for three to four days while buprenorphine is cleared from the body
            2. Reassess analgesia daily and expect to decrease full agonist between days three and four
            3. Manage acute pain with a tapering regimen
        ii. Patient should be opioid-free for 24-hours before restarting buprenorphine to avoid withdrawal.
2. In acute traumatic presentation
    a. Conversion to methadone according to conversion tables and titrate dose to effect
    b. When clinical presentation does not afford conversion and titration, recommend aggressive acute titration to full opioid agonist.
        i. High doses are required to displace high affinity buprenorphine from μ-receptors
        ii. Requires continuous cardiopulmonary monitoring

Naltrexone *(opioid antagonist often used to limit relapse following opioid dependence rehabilitation)*

Due to its antagonist mechanism, naltrexone creates a difficult clinical scenario, particularly in the acute traumatic setting. Naltrexone reduces opioid sensitivity by blocking receptors, but also upregulates μ-receptors. During initial treatment of post-injury and perioperative pain, a patient may not be sensitive to a short-acting μ-agonist and may require many times the normal dose.[226] After two weeks, sensitivity to opioids may increase, risking overdose. When the acute pain period is over, and naltrexone is restarted, it carries the risk of inducing withdrawal. Therefore, the recommendation is to consult addiction medicine, acute pain service, or psychiatry.

NSAIDS and Fracture Healing

- The panel recommends for the routine use of NSAIDs as part of a comprehensive analgesic plan for operative and non-operative fracture care (strong recommendation, low quality evidence).

One of the major barriers to using non-narcotic analgesics in orthopaedic trauma has been the reluctance to employ nonsteroidal anti-inflammatory drugs (NSAIDs) in the setting of fracture or arthrodesis surgery of any kind. For decades, NSAIDs were avoided due to fears about bone healing. However, a review of the evidence has found the data on the effect of NSAIDs on bone healing too conflicting to make a clinical recommendation one way or the other.[227-229] Given the proven track record of NSAIDs in alleviating musculoskeletal pain, withholding NSAIDs from our analgesic armamentarium is a significant disadvantage. Under the current circumstances, the basis of this prohibition merits a critical review.

The basic science studies have been conflicting, at best. The most rigorous basic science studies are animal models of spinal fusion, while fracture healing models yielded mixed results at best.[230] Endpoints for animal studies demonstrated that NSAIDs contributed to reduced mechanical strength (as bone stiffness and load to failure) and delayed time to union.[231, 232] Nonetheless, this lack of clarity has re-enforced the perception of a deleterious effect. Further animal studies attempted to examine what the possible mechanism of action could be, and tried to establish if there was a lesser impact from COX-2 specific inhibitors compared to indomethacin in the animal setting, again with mixed results.[232, 233]

Clinical studies are similarly unclear, but four of the clinical papers should be examined critically as they are frequently cited when raising alarm over NSAIDs in fracture healing. Giannoudis et al. used a retrospective case-control model to compare femoral shaft fractures that had not healed to a group that healed successfully.[234] The odds ratio for nonunion with the use of NSAIDs was reported as a disturbingly high 10.7 (95% CI: 3.55, 33.23), but the study was small and underpowered (sample size of 32 patients), NSAID use was severely underrepresented in the control group, and this same sample showed no effect of smoking. Further, by starting with a group of 32 non-united diaphyseal femur fractures, investigators may well have been preselecting the group most likely to take NSAIDs (for the pain of nonunion). Bhattacharyya et al. point out exactly this bias when discussing their finding of higher NSAID use in the subset of humerus fractures that were treated closed and did not heal.[235] To avoid selection bias, Bhattacharyya's group queried Medicare data (1995-2000) from two states for patients with a humeral shaft fracture. Starting with nearly 10,000 records, they found 104 patients (1.1%) with a nonunion. They reported that patients who used NSAIDs or opioids within the first 90 days after fracture had relative risks for nonunion of 3.7 (95%CI:2.4, 5.6) or 1.6 (95%CI: 1.1,2.5)

respectively.[235] More recently, Jeffcoach and co-workers retrospectively reviewed long bone fractures over a two-year period at a single trauma center. The patients who suffered a long bone fracture and received NSAIDs during the inpatient postoperative days (12% of 1901 patients) had an odds ratio for a complication (nonunion, malunion, infection) of 2.17 (1.15-4.10).[236] In a well-designed, prospective randomized trial on different durations of indomethacin treatment (three days, one week, or six weeks) for prophylaxis of heterotopic ossification, Sagi et al. showed that at six months after surgery, the highest incidence of nonunion of the posterior acetabular wall (67%) occurred in the group with the longest duration (six weeks) of indomethacin use.[237] While there were only thirteen patients in this group and that raises concerns over adequate power, the rate of nonunion of the posterior wall in all groups was surprisingly high.

While isolated clinical investigations such as these have been cited as evidence to withhold NSAIDs during fracture treatment, this conclusion is not supported by a critical examination of the existing literature. Two recent comprehensive meta-analyses by Kurmis et al.[229] and Marquez-Lara et al.[238] have concluded that while some animal studies may raise a concern, there is no high-quality literature support for NSAID inhibition of fracture healing in the clinical setting. Ultimately, these critical evaluations of the existing clinical literature must stand as the cornerstones of our practice guideline recommendations on this issue.

Based on the unknown clinical role of opioids on fracture healing, recent investigations have tried to examine a potential effect of opiate analgesics on fracture healing. Morphine has been demonstrated to inhibit osteocalcin in vitro.[239] Chrastil et al. used a rat model to examine opioid influence on femur fractures and found that animals treated with opiate analgesia formed callus in greater volume, but that this callus was more disorganized and mechanically weaker

than the control animals.[240] OPIAD (Opiate Induced Androgen Deficiency) Syndrome describes the naturally occurring reduction in serum testosterone seen clinically with both acute and chronic opioid administration[241] and Brinker et al. have previously demonstrated hypogonadism to be among the metabolic abnormalities identified in patients with nonunion.[242] Chrastil and co-workers attempted to determine if supplemental testosterone might be used to mitigate the effects of opioids on callus formation and strength, but they found supplemental testosterone was ineffective for this purpose.[243] This study casts doubt on the theory that the effect of opioids on bone healing is solely mediated by hypogonadism, since the opioid-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 opioids in bone healing are very preliminary, and have not been corroborated with quality clinical studies, but given its potential impact on clinical practice, the field certainly merits further bench and clinical investigation.

With regards to the effectiveness of NSAIDs for pain control, there are now some head-to-head clinical comparisons available between NSAIDs and opioids for the acute management of musculoskeletal complaints in both the pediatric[244] and adult[245, 246] populations. To date, these studies have demonstrated NSAIDs to provide equally effective analgesia.

To summarize, there is simply no conclusive clinical evidence to prohibit the use of NSAIDs in fracture care. Further, risks to the population from oral opioid use, and the prolonged use after resolution of musculoskeletal injury, are well-established. NSAIDs also provide effective analgesia in the setting of musculoskeletal pain.[247] Taking all of these factors and the existing clinical evidence into account, we recommend the routine use of NSAIDs as part of a comprehensive analgesic plan for operative and non-operative fracture care.

Nerve/Regional/Field Blocks

This section is organized around the following three time periods: (1) During a hospital admission prior to fracture surgery; (2) Intraoperatively and the immediate post-operative period (3); The remote (>3 months) post-operative period. In each of these temporal periods, in relation to fracture surgery, we asked what is the evidence that nerve, or regional, or field blocks improve pain control and decrease use of opioids?

During a hospital admission prior to fracture surgery

- The panel recommends that regional nerve blocks (femoral nerve or fascia iliaca) should be placed in patients with acute hip fractures at the time of presentation to the Emergency Department (strong recommendation, high quality evidence).

The evidence for this recommendation is confined to hip fracture patients. Multiple studies show that nerve blocks placed in the emergency department (ED) can be accomplished by trained personal with minimal risks or complications.[248-258] These blocks have consistently been found to be effective in comparison to standard of care (parenteral opioids alone) in decreasing opioid use and improving patient's pain in the pre-operative period.[248, 251, 252, 254, 256, 257] These results have been confirmed in multiple RCTs and some of these studies are placebo-controlled with blinded assessment of the outcome.[252, 253, 257] Although there is high-quality evidence for these benefits of nerve blocks, instituting routine nerve blocks for hip fracture patients cannot be accomplished by the surgeon in isolation. System-wide changes in practice with involvement of other care providers (emergency medicine and anesthesia) are required.

There are other possible benefits of ED regional nerve blocks for hip fracture patients. One RCT found that these blocks decrease the incidence of delirium in hip fracture patients who are at intermediate risk for this condition.[257] Another RCT found a functional post-operative

benefit in the hospital (walking distance and stair climbing ability) that lasted until six weeks after surgery.[256] There is less strength of evidence for these benefits because they have only been assessed in one study each.

The nerve block technique has varied between studies. Some studies have utilized a three-in-one femoral nerve block while others recommend a fascia iliaca block. Most studies recommend ultrasound guidance for either type of block.[249, 255] The fascia iliaca compartment block requires less precision and is probably more easily learned. The location is more remote from the neurovascular bundle and thus nearly eliminates the risk of intraarterial injection. Femoral nerve and fascia iliaca blocks have also been shown to have similar efficacy in total knee arthroplasty patients.[250] Recommended training has been 30 minutes of didactic training followed by variable periods of practice and supervised clinical performance. This short duration of training, however, may assume preexisting ultrasound skills.[249, 252]

Five studies have compared "standard" preoperative MMA to the addition of a nerve block. Addition of a femoral nerve block to preoperative oxycontin and celecoxib did not make a difference in total knee arthroplasty patients.[259] YaDeau, et al., however, showed lower visual analog pain scales (VAS) with addition of a femoral nerve block to standard epidural anesthesia.[260] Divella's group evaluated resting and dynamic VAS scores for three days after total hip arthroplasty. Pain control was oxycontin and acetaminophen versus continuous epidural levobupivacaine. Resting VAS scores between the two groups were similar for days one and two, but VAS scores were significantly lower on day three for patients in the oxycontin group. Dynamic VAS scores for the oxycontin group were higher on day one and lower on day three.[261] The use of general anesthesia with preoperative oxycodone and celecoxib versus intrathecal bupivacaine, morphine, and clonidine showed higher pain scores, faster time to first rescue

668 medication need, and longer length of stay in the general anesthesia group.[262] Addition of
669 multimodal postoperative pain medication (including oxycodone, tramadol, and ketorolac)
670 compared to parenteral patient-controlled analgesia showed less narcotic consumption, lower
671 pain scores, and higher satisfaction as well as higher physical therapy goal achievement in the
672 MMA group.[263]

673 The studies reviewed have not reported any complications of blocks, but most admit that
674 the study was not powered to detect rare complications. Clinicians should be aware of the
675 possibility of complications such as inadvertent intravascular injection, infection, intraneural
676 injection, and masking symptoms of compartment syndrome.[251] All studies report a rapid onset
677 of pain relief from these blocks, however the effect is often not complete and adjunctive
678 analgesics are often necessary.[252]

679 **Intraoperatively and the immediate post-operative period**

680 • The panel recommends that clinicians consider local or regional block anesthesia during
681 operative treatment of fractures and as part of the post-operative multimodality pain
682 control regimen. (strong recommendation, high quality evidence)
683 • The panel recommends that if a block is going to be performed for intraoperative and
684 post-operative pain control, a continuous catheter be considered over a single-shot block
685 to better facilitate post-operative pain control and diminish rebound pain. (conditional
686 recommendation; moderate quality evidence)

687 The use of peripheral anesthesia via local injections, field blocks, single-shot regional blocks
688 and indwelling catheter regional blocks have all been shown to decrease pain scores and opioid
689 consumption in the immediate and short-term perioperative period. The bulk of this data comes
690 from the arthroplasty literature with contributing papers from the sports medicine, foot and

691 ankle, and trauma literature.[264] The data outside the orthopaedic literature is even more robust.
692 Problems with these lower extremity blocks include a possible increase in rate of falls and
693 rebound pain that has been reported in some studies.

694 Five articles have compared various periarticular injections. Early postoperative pain
695 scores and opioid usage were lower with continuous femoral nerve catheter plus sciatic block
696 than with periarticular injection with ropivicaine or liposomal bupivacaine.[265] Ng and colleagues,
697 however, found equivalent outcomes with femoral nerve catheter versus periarticular injection.[266]
698 In addition, periarticular injection alone was not superior to post-operative epidural analgesia for
699 pain control.[267] The addition of periarticular liposomal bupivacaine to a periarticular injection
700 cocktail was more effective than ropivacaine at 6 and 12 hours postoperatively, however
701 intrathecal morphine was more effective at six hours.[268] Addition of ropivacaine and ketorolac to
702 a periarticular injection cocktail improved postoperative pain control.[269]

703 In one RCT, a significant decrease in opioid consumption and better pain scores were
704 found at 48-hours after hip arthroscopy in patients who received a femoral nerve block (FNB)
705 versus general anesthesia (GA). However, the FNB group had a significant increase in rate of
706 falls compared to the GA group highlighting one of the risks of this type of anesthesia which in
707 part accounts for its moderate recommendation.[270]

708 In another RCT, the benefit of local injection was assessed. A significant decrease in pain
709 scores and opioid consumption was found for eight hours and trended less over 48 hours in
710 patients receiving a local injection compared to general anesthesia alone for femur fractures. The
711 injection (containing ropivicaine, morphine, and epinephrine) was administered at the time of
712 surgical fixation of the fracture. There were no complications attributed to the local injection
713 itself.[197]

Pre-operative sciatic or popliteal continuous peripheral nerve block (CPNB) were compared to post-operative patient-controlled analgesia (PCA) in a retrospective study of patients undergoing fixation of talus and calcaneal fractures. While Numerical Rating System pain scores, duration of stay, and side effects were equivalent in the two groups over 72-hours, morphine equivalent consumption on post-operative day one by the PCA patients was 30-fold that of the CPNB patients. [271]

A single-shot popliteal block was compared to an intraoperative ankle block in a RCT of patients undergoing elective forefoot surgery. The length of block time in the popliteal block group was 44% longer than the ankle block group. While the patient satisfaction and perceived effectiveness with both types of blocks was similar, the popliteal block group showed significantly lower VAS pain scores the night after surgery and throughout the next morning. [272]

In an RCT of patients undergoing open reduction and internal fixation of distal radius fractures, GA patients needed more IV pain medications in the PACU compared to those who received a single-shot brachial plexus block. In the 12 to 24 hours after surgery, patients who received the block showed a more aggressive rise in VAS scores and narcotic use consistent with the block wearing off and the patients experiencing rebound pain. Ultimately, the GA group had a statistically significantly higher total narcotic use at 72 hours compared to the block group.[273]

Peripheral anesthesia in the form of a block can be administered either via a single-shot injection or by placing a catheter that has the ability to deliver anesthetic around the nerve in a continuous fashion until the catheter is removed. Rebound pain is the pain a patient experiences when the block wears off and can be quite significant. This is typically because the patient has not been taking other post-operative pain medications due to low pain scores during the duration that the block has been in effect.

Goldstein et al. addressed the problem of rebound pain phenomenon and were one of the first groups to write about this effect.[274] They compared a single-shot popliteal block to general anesthesia (GA) in an RCT of patients undergoing fixation of ankle fractures. Significantly lower pain scores were reported for the block group at 2, 4, and 8 hours after surgery, but significantly better pain scores were found in the GA group from 8 to 24 hours.

There is some evidence that continuous catheters control pain for a longer duration of time and may help diminish rebound pain by allowing the patient to get farther in the recovery process. In one RCT, a single-shot popliteal (SSP) block was compared to a continuous popliteal block (CPNB) in patients undergoing fixation of unstable ankle fractures. The CPNB catheter was removed at 48 hours. Over the first 72 hours, patients in the CPNB group took significantly fewer oral narcotics and had lower pain scores.[275] Another study of patients undergoing open fixation for calcaneal fractures compared controls (no regional blocks) vs. a single-shot block or against a continuous popliteal nerve block. In the 36 hours after surgery, the patients in the continuous block used significantly fewer IV narcotics than did the other two groups. However, a limitation of this study was that their post-operative pain protocol changed multiple times during the course of the study. [276]

The remote (>3 months) post-operative period

- The panel makes no recommendations for this time period, as we were unable to find any data to guide us on whether regional or local anesthesia performed before, during, or in the immediate post-operative period has any effect on improving pain scores or decreasing opioid consumption at this time frame. (no recommendation, no evidence)

Pain/Sedation Assessment

Inpatient Pain Assessment

- The panel recommends regular assessment of pain for both inpatients and outpatients in order to evaluate the need for initiation or continuation of opioid therapy (strong recommendation, low quality evidence).

Effective January 1, 2018, the Joint Commission required new and revised pain assessment and management standards to improve quality and safety of care.[277] The requirements speak to (1) prioritization of pain assessment and management as an organizational priority; (2) establishment of medical staff in leadership roles to address performance improvement activities related to patient safety; (3) assessment and management of patient pain and minimization of risks associated with treatment with opioids; (4) data collection to monitor performance related to patient safety; and (5) compilation and analysis of data to inform continued performance improvement.

Inpatient Pain Assessment

- The panel recommends that sedation assessment be conducted by nursing staff on all inpatients prior to and following administration of an opioid medication (strong recommendation, low quality evidence).

In 2012, The Joint Commission issued a warning regarding adverse drug events associated with opioid analgesics, most importantly respiratory depression, among patients in the inpatient hospital setting.[278] The incidence of opioid-induced respiratory depression ranges from 0.1 to 37%.[279] Nurses are typically the first to detect respiratory depression.[280] One cause for opioid-related adverse events, however, is inadequate monitoring of patients administered opioids, occurring in about a third of cases.[278, 280] Patient monitoring includes sedation assessments,

781 frequency and quality of respirations, and electronic methods such as pulse oximetry. A survey
782 of nurses belonging to the American Society for Pain Management Nursing[281] indicated nurses
783 find sedation scales and watching the patient to be more useful than electronic methods.
784 However, while there is no evidence to inform the frequency of monitoring, sedation scale scores
785 should be a major consideration in the decision to administer opioids for pain management. It is
786 important to monitor sedation as it is an indicator of impending opioid-induced respiratory
787 depression; detecting over-sedation can prevent a more clinically significant adverse event. The
788 Pasero Opioid-induced Sedation Scale[282] (Table 5), which has been validated for assessing
789 sedation during opioid administration,[283] is an example of a tool that can be used by nurses to
790 assess patients prior to and following administration of prescription opioids.[284]

791
792 Insert Table 5 near here

793 **Naloxone**

794 • The panel recommends co-prescribing of naloxone when factors that increase risk of
795 overdose are present (strong recommendation, low quality evidence).

796 For patients prescribed opioids, risk mitigation strategies are an important consideration.
797 While limited evidence exists on the outcomes of prescribing naloxone in combination with
798 opioids, distribution via community-based harm reduction programs have demonstrated
799 decreased risk of death due to opioid overdose.[285-288] The majority of programs, however, have
800 been conducted with illicit use populations with a focus on harm reduction as opposed to a
801 patient safety focus for patients prescribed opioids for acute or chronic conditions. The *CDC*
802 *Guideline for Prescribing Opioids for Chronic Pain*[25] recommend co-prescribing or offering
803 naloxone to patients with increased risk for opioid overdose who are prescribed opioids. These

risk factors include history of overdose or substance use disorder history, opioid dosages ≥50 MME/day, or co-prescribing with benzodiazepines.

System Strategies

Prescription Drug Monitoring Programs

- The panel recommends that all prescribers register to gain access to their state's Prescription Drug Monitoring Program (PDMP) and regularly query the PDMP before prescribing opioids (strong recommendation, low quality evidence).

Prescription Drug Monitoring Programs (PDMPs) are databases that track scheduled medications dispensed from pharmacies. The databases were developed to reduce prescription drug misuse and diversion. The conceptual model of PDMPs assumes that increased monitoring of opioid prescriptions is associated with changes in opioid prescribing behavior, opioid diversion and supply, as well as opioid-related morbidity and mortality.[289] Numerous unintended consequences of PDMPs have been described in the literature and include the following: (1) potential decrease in legitimate prescribing; (2) patient privacy concerns; (3) inability to connect patients with known aberrant use to resources; (4) potential increase in illegal prescription drug activity or users switching to other substances such as heroin; (5) further reduced patient visit time due to time required to check PDMP; and (6) potential decrease in patient satisfaction ratings.[290] Finally, PDMPs vary tremendously from state-to-state based on (1) the number of schedules included; (2) the frequency of updates; (3) housing entities; (4) accessibility; (5) access requirements; (6) reactive and proactive reporting; (7) associated prescriber education; and (8) interstate data sharing.[290]

826 Four reviews of PDMPs have been published to date[289-292] with the most recent one
827 synthesizing articles published through 2015.[289] Worley et al. concluded that PDMPs were
828 associated with lower substance abuse treatment admission rates, fewer opioid prescriptions, less
829 diversion, and less "doctor shopping". The authors acknowledge, however, that results depend on
830 the specific components of each unique PDMP and that evidence is limited.[291] Haegerich et al.
831 believe PDMPs to be effective, but that effect sizes from the papers they reviewed were
832 generally very low and may depend on specific PDMP components such as mandatory review or
833 proactive reporting.[292] Gugelmann et al. concluded that PDMPs seem to have benefits including
834 reduced per capita supply of opioids and fewer incidents reported to poison control centers,
835 however, there are also studies showing no effect.[290] Finally, Finley et al. found no consistent
836 pattern, with efficacy varying by state.[289]
837 Several articles on PDMP efficacy have been published since 2015, and the results have been
838 mixed as well. The Florida PDMP was associated with a 25% decline in oxycodone-caused
839 deaths.[293], but a multi-state study found PDMPs were not associated with reduction in overdose
840 deaths and were, in fact, sometimes associated with increased mortality from non-prescription
841 opioid drugs, such as heroin.[294] There was also evidence of increased ED visits for heroin
842 overdoses in New York, while visits for prescription opioid overdose leveled.[295] In contrast,
843 Dowell and colleagues found "relatively large but statistically insignificant reductions" in heroin
844 overdose deaths, indicating that perhaps a decrease in opioids does not lead to an increase in
845 heroin use.[25]
846 Three studies on PDMP implementation found no association with decreased opioid
847 prescribing [296-298] while three others found that PDMP implementation reduced opioid
848 prescriptions [25, 299, 300] and overdose deaths.[25] Some studies found PDMPs to be effective in

specific groups, such as patients with multiple provider episodes (i.e., 'doctor shopping') whose prescribers were sent an unsolicited report by the state,[301] Medicare Part D enrollees,[302] and Medicaid patients.[299] Finally, due to the variability in PDMPs by state, one study rated the strength of the PDMP and found that a 1% increase in PDMP strength was associated with a 1% decrease in overdose deaths, indicating room for improvement in outcomes for PDMPs of lower strength.[303]

While the literature remains inconsistent, PDMPs are a promising intervention, especially when the PDMPs are of robust strength. We recommend checking the PDMP prior to prescribing. Steps must be taken, however, to alleviate the potential consequences of curtailing prescribing based on the results of a PDMP search, particularly the potential for patients to switch to heroin. Therefore, we recommend referring patients to behavioral health and addiction medicine if the PDMP indicates aberrant behaviors. Furthermore, the evidence does demonstrate that PDMPs are not a panacea for preventing prescription opioid misuse, abuse, and diversion.

Prescriber and Patient Education

- The panel recommends that departments support opioid education efforts for prescribers and patients (strong recommendation, moderate quality evidence).

Physicians often lack training in pain management and addiction; 59% of physicians report medical school preparation regarding chronic pain treatment as "fair" or "poor"[304], and median instruction time spent on pain education in US medical schools is 11.1 hours, compared to 27.6 hours in Canada.[305] After graduate medical education, only five states (CT, IA, MD, SC, TN) require physicians to obtain periodic CME on prescribing, substance use disorders, or pain management.[306]

The effectiveness of educational interventions for physicians is strong. A synthesis of reviews on CME education find that studies on CME interventions consistently show improvement in both physician performance and patient health outcomes.[307] The most effective CME sessions are interactive, use multiple methods, involve multiple exposures, and are longer.[307] After New Mexico began requiring CME in 2012-2013 about pain and addiction along with required PDMP registration and query, the state saw statistically significant increased physician knowledge, self-efficacy, and attitudes, as well as a decrease in both statewide morphine milligram equivalents dispensed and drug overdose deaths.[308] Online educational interventions have been moderately effective.[309] Education in conjunction with clinical decision support is also effective at changing naloxone prescribing rates.[310]

Other strategies described in the literature include brief one-on-one physician education,[311, 312] development and dissemination of guidelines and policies,[313, 314] and Risk Evaluation and Mitigation Strategy (REMS).[315] Public health detailing is an approach based on the pharmaceutical sales strategy, by which messages are pushed using brief one-on-one educational visits during the normal workflow. Staten Island saw a reduction in high-dose prescribing and stabilizing of days' supply after implementing this strategy.[311] Similarly, an ED in Australia delivered one-on-one education via a clinical champion and was very effective at improving information given to patients, increasing notifications sent to general practitioners, reducing total dose prescribed, and incorporating non-opioid therapies.[312] This approach is, however, resource intensive and has a limited scope of impact.

Development of department guidelines, policies, or both is another option. Hill et al. described an intervention within surgical specialties at an academic medical center which included dissemination of operation-specific opioid prescribing guidelines. This intervention

significantly reduced the number of pills prescribed.[313] When a similar approach was implemented in the emergency department setting the number of patients prescribed opioids and number of pills prescribed decreased by 40% and 15%, respectively, with reductions sustained over 2.5 years.[314] Finally, Risk Evaluation and Mitigation Strategies (REMS) developed by the FDA in 2007 required pharmaceutical manufacturers to take steps to reduce risks associated with the medication. Strategies can include medication guides for patients, clinician education, and physician certification.[316] Both immediate release and extended release opioids are now subject to these regulations.[317] Thus, manufacturers are required to fund continuing education regarding opioid prescribing. Overall, the resulting SCOPE of Pain educational program has been shown to increase physician knowledge and reported intention to change practice.[318] The SCOPE of Pain program has also implemented a "train the trainer" approach which facilitates wide dissemination of information.[315] Physicians are advised to be aware of potential conflicts of interest when attending pharmaceutical company-funded sessions.[319]

Overall, education is a necessary, but insufficient, approach to improving prescribing and patient outcomes. In addition, the literature is mostly limited to opioids for chronic pain management rather than acute or post-surgical pain. Regardless, we recommend supporting opioid education efforts both in graduate medical education and through continuing education.

Literature that focuses on evaluating the effects of patient education is limited, but the few studies conducted support effective patient education. Strategies included educational pamphlets,[320-322] web-based interactive education,[323] and clinician-delivered education.[324, 325] All interventions that included knowledge as an outcome demonstrated a significant effect,[320, 322, 323, 325] and many studies observed changes in risky behaviors, such as sharing pills,[320, 323] pill

storage,[320] saving and disposal of pills,[320, 321, 323, 324] driving[322] and taking more medication than prescribed.[323]

Clinical Decision Support

- The panel recommends that prescribers, to the extent possible, develop, support, or both the implementation of clinical decision support regarding opioid prescribing in the electronic medical record (strong recommendation, low-quality evidence).

We reviewed the literature on the impact of clinical informatics interventions on opioid prescribing. A total of 14 articles were identified that included prescribing outcomes and the quality of the evidence was low. Most of the studies used study designs that did not have any concurrent control group. This is a significant weakness due to the national attention surrounding the opioid crisis currently in lay press, politics, and medicine. Without concurrent controls, the effects seen after implementation of these interventions could be overestimates if prescribing was already decreasing due to the current climate around opioids. There were, however, two randomized controlled trials that demonstrated an effect on some outcomes.[326, 327] Most of the 14 studies included patients in the emergency department[326, 328-331] or specifically for patients receiving chronic opioid therapy.[327, 332-334] Only one study assessed clinical decision support in an orthopaedic surgery population.[335]

There is a gap in the literature surrounding acute pain outside of the emergency room, other than after cesarean section[336] and following hand surgery.[335] This is an important area of research since a short course of opioid treatment for acute pain can often result in chronic opioid therapy.[9]

All of these studies were conducted in urban settings or across a wide area including both urban and rural settings. It is critical to study these interventions in rural areas since they are substantially burdened with this epidemic.[337] In addition, prescriber response to these

939 interventions may differ in outlying hospitals and in practices that are not part of an academic
940 hospital where prescribers are consistently exposed to new literature, new techniques, and other
941 clinical innovations. In addition, numerous articles were identified that described clinical
942 decision support regarding opioids but did not report on outcomes of the intervention.

943 While these feasibility and implementation articles are important for fully describing
944 interventions, decisions cannot be made regarding continuation, iterative improvement, or
945 adoption of the intervention by another institution without evidence of efficacy. The lack of
946 follow-up outcomes papers could represent publication bias, whereby articles in the literature are
947 more likely to have been effective. For example, only one study found no effect of the
948 intervention[331] while the rest of the interventions were effective,[328, 329, 332-334, 336, 338, 339] or mixed
949 (had effect on some outcomes but not all).[326, 327, 330, 335, 340] Finally, most studies included
950 outcomes associated with prescriptions (i.e. number of prescriptions, number of pills, average
951 dose, number of risky concurrent prescriptions for opioids with benzodiazepines, number of
952 extended release prescriptions).[326, 328, 330, 331, 335, 336, 338-340] Others measured outcomes associated
953 with safe prescribing (i.e. urine drug screens, treatment agreement, functional assessments, risk
954 assessments, documented diagnosis).[327, 329, 332-334] The conceptual framework implicitly presented
955 is that these interventions lead to safer prescribing practices that lead to fewer high risk
956 prescriptions that in turn ultimately reduces risk of misuse, abuse, or diversion of prescription
957 opioids. However, no studies measured rates of overdose, opioid use disorder, or other outcomes
958 to demonstrate this pathway.

959 Despite the low-quality evidence, we strongly recommend pursuing clinical decision support
960 to the extent possible. Potential approaches include power plans/order sets,[331, 335, 340]

961 dashboards,[332, 338, 339] risk assessment and screening,[327, 329, 333] alerts,[326, 328, 330] and other decision
962 support.[334, 336, 339]

963 Order set interventions could include recommended pain management regimens and dosing
964 based on patient characteristics,[340] prepopulating the dosing at a minimum rather than a range
965 (i.e. one pill 4x per day rather than 1-2 pills 4-6 times per day).[335], and including non-opioid
966 medication options.[335]

967 Dashboards are useful for tracking physician adherence to guidelines and protocols. They are
968 particularly useful because they provide actionable information to the prescriber.[341] For example,
969 a prescriber can see what patients are due for a certain screening and conduct the appropriate
970 screening at the patient's next visit. Dashboards can also promote transparency, accountability,
971 and natural competition by which prescribers compare their statistics to those of their partners,
972 leading to improved performance.[342] Dashboards vary in the metrics tracked (e.g., urine drug
973 screens, pain agreements, functional status assessment, visits with behavioral health providers,
974 high dose opioids, and concurrent opioids and benzodiazepines).[332, 338] Dashboards also vary
975 regarding the level of integration into workflow. Some are housed on the intranet for prescribers
976 to access on-demand[332] while others are "pushed" to prescribers at defined time intervals.[332, 338]

977 Many risk assessment tools are accessible that indicate risk for opioid abuse, misuse, and
978 diversion. Available tools include the Opioid Risk Tool[343] the Screener and Opioid Assessment
979 for Patients with Pain (SOAPP-R),[344] the Drug Abuse Screening Test (DAST),[345] the Brief Risk
980 Interview,[346] and the Current Opioid Misuse Measure (COMM).[347] Additionally, guidelines
981 recommend that providers screen patients prior to prescribing opioids although the CDC
982 guidelines caution against placing full confidence in the sensitivity and specificity of these
983 screening tools because consequences of underestimation or overestimation of risk can be

significant.[348] An electronic risk assessment program called Pain Assessment Interview Network, Clinical Advisory System (PainCAS)[327, 333] is completed by the patient prior to their visit, either at home or upon registration at the clinic, and includes the SOAPP-R and COMM, both validated instruments. Once completed, administrative staff uploads the report to that patient's electronic medical record. Another electronic assessment is a short 3-item screening for tobacco, alcohol, and drug use that is programmed into the electronic triage tool in the ED.[329] These studies report significant increase in screening and documentation, however, their use does not appear to alter patient clinical outcomes.

Alerts were originally developed to reduce adverse drug events by alerting the provider to contraindications or allergies associated with medications.[349-351] Since then, alerts have been developed for additional situations, including opioids risk. It is critical when developing alerts to ensure information is meaningful and does not trigger at unacceptable rates, thus causing "alert fatigue".[352] Alerts may include patient risk factors,[328] suggest non-opioid medications or non-pharmaceutical modalities,[328] inform the prescriber that the patient was referred to pain management,[330] or inform the prescriber that the patient has an existing opioid care plan.[326]

Other examples of decision support implemented in the included articles include "smart set" documentation, a patient-facing tablet decision aid, and comprehensive prescribing tools. "Smart set" documentation standardizes practices by walking prescribers through the appropriate prescribing policies.[334] Similarly, another study described implementation of a large set of decision aids into the EMR as part of Safe and Appropriate Opioid Prescribing Program (SAOP).[339] Aids included medication menus, medication alerts, preferred and maximum doses, links to guidelines, prompts for alternative treatments and medications, patient treatment agreements, and a link to the PDMP. Finally, one article discussed a patient-facing decision aid

in which patients used a tablet-based decision tool to learn about post-cesarean pain and oxycodone to guide her in making decisions about the number of pills she wanted.[336]

These approaches are promising interventions to improve patient safety and reduce opioid prescribing. Many of these interventions included multiple components in addition to the electronic tool such as pocket cards, educational sessions, prescribing policies, care plans, and patient-facing pain policies.[326, 328, 335, 339, 340] While a multi-pronged intervention has greater likelihood of success, it is challenging to identify the unique contribution of the electronic tool in each case.

CONCLUSIONS

Balancing comfort and patient safety following acute musculoskeletal injury is possible when utilizing a true multimodal approach including cognitive, physical, and pharmaceutical strategies. In this document, we attempt to provide practical, evidence-based guidance for clinicians in both the operative and non-operative settings to address acute pain from musculoskeletal injury. We also organized and graded the evidence to both support recommendations and identify gap areas for future research.

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REFERENCES

1. Rudd R, Aleshire N, Zibbell J, et al. Increases in Drug and Opioid Overdose Deaths -- United States, 2000-2014. MMWR. 2016;64:1378-1382.

2. Rudd RA, Seth P, David F, et al. Increases in Drug and Opioid-Involved Overdose Deaths - United States, 2010-2015. MMWR Morb Mortal Wkly Rep. 2016;65:1445-1452.

3. Dowell D, Arias E, Kochanek K, et al. Contribution of opioid-involved poisoning to the change in life expectancy in the United States, 2000-2015. JAMA. 2017;318:1065-1067.

4. Centers for Disease Control and Prevention. Prescribing Data. Available at: www.cdc.gov/drugoverdose/data/prescribing.html. Accessed September 20.

5. Volkow ND, McLellan TA, Cotto JH. Characteristics of opioid prescriptions in 2009. JAMA. 2011;305:1299-1300.

6. Daubresse M, Chang H, Yu Y, et al. Ambulatory diagnosis and treatment of nonmalignant pain in the United States, 2000-2010. Med Care. 2013;51:870-878.

7. Bicket MC, Long JJ, Pronovost PJ, et al. Prescription Opioid Analgesics Commonly Unused After Surgery: A Systematic Review. JAMA Surg. 2017;152:1066-1071.

8. Kim N, Matzon JL, Abboudi J, et al. A Prospective Evaluation of Opioid Utilization After Upper-Extremity Surgical Procedures: Identifying Consumption Patterns and Determining Prescribing Guidelines. J Bone Joint Surg Am. 2016;98:e89.

9. Hooten WM, St Sauver JL, McGree ME, et al. Incidence and risk factors for progression from short-term to episodic or long-term opioid prescribing: A population-based study. Mayo Clin Proc. 2015;90:850-856.

10. Braden J, Fan M, Edlund M, et al. Trends in use of opioids by noncancer pain type 2000-2005 among Arkansas Medicaid and HealthCore enrollees: results from the TROUP study. J Pain. 2008;9:1026-1035.

11. Martin BC, Fan MY, Edlund MJ, et al. Long-term chronic opioid therapy discontinuation rates from the TROUP study. J Gen Intern Med. 2011;26:1450-1457.

12. Von Korff M, Saunders K, Thomas Ray G, et al. De facto long term opioid therapy for noncancer pain. Clin J Pain. 2008;24:521-527.

13. GRADE Working Group. The Grading of Recommendations Assessment, Development and Evaluation. Available at: http://www.gradeworkinggroup.org/. Accessed October 15, 2017.

14. American Academy of Family Physicians. AAFP Chronic Pain Management Toolkit. Available at: https://www.aafp.org/dam/AAFP/documents/patient_care/pain_management/cpm-toolkit.pdf. Accessed August 22, 2018.

15. American Academy of Orthopaedic Surgeons. Pain Relief Toolkit. Available at: https://www.aaos.org/Quality/PainReliefToolkit/?ssopc=1. Accessed October 15, 2017.

16. American Academy of Pain Medicine. Use of Opioids for the Treatment of Chronic Pain: A Statement from the American Academy of Pain Medicine. Available at: http://www.painmed.org/files/use-of-opioids-for-the-treatment-of-chronic-pain.pdf. Accessed October 1, 2017.

17. American College of Obstetricians and Gynecologists. ACOG Committee Opinion Summary. Opioid Use and Opioid Use Disorder in Pregnancy. Available at: https://www.acog.org/Clinical-Guidance-and-Publications/Committee-Opinions/Committee-on-Obstetric-Practice/Opioid-Use-and-Opioid-Use-Disorder-in-Pregnancy. Accessed October 1, 2017.

18. American Society of Addiction Medicine. ASAM National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use. Available at: https://www.asam.org/docs/default-source/practice-support/guidelines-and-consensus-docs/asam-national-practice-guideline-supplement.pdf. Accessed October 1, 2017.

19. American Society of Anesthesiologists Task Force on Acute Pain Management. Practice Guidelines for Acute Pain Management in the Perioperative Setting: An Updated Report by the American Society of Anesthesiologists Task Force on Acute Pain Management. Anesthesiology. 2012;116:248-273.

20. American Society of Anesthesiologists Task Force on Neuraxial Opioids, American Society of Regional Anesthesia and Pain Medicine. Practice Guidelines for the Prevention, Detection, and Management of Respiratory Depression Associated with Neuraxial Opioid Administration: An Updated Report by the American Society of Anesthesiologists Task Force on Neuraxial Opioids and the American Society of Regional Anesthesia and Pain Medicine. Anesthesiology. 2016;124:535-552.

21. Busse JW, Guyatt G, Carrasco A, et al. The 2017 Canadian guideline for opioids for chronic non-cancer pain. Available at: http://nationalpaincentre.mcmaster.ca/documents/Opioid%20GL%20for%20CMAJ_01may2017.pdf. Accessed October 15, 2017.

22. Centers for Disease Control and Prevention. Pocket Guide: Tapering Opioids for Chronic Pain. Available at: https://www.cdc.gov/drugoverdose/pdf/clinical_pocket_guide_tapering-a.pdf. Accessed January 15, 2018.

23. Centers for Disease Control and Prevention. Calculating Total Daily Dose of Opioids for Safer Dosage. Available at: https://www.cdc.gov/drugoverdose/pdf/calculating_total_daily_dose-a.pdf. Accessed 22 Aug 2018.

24. Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain. 2009;10:113-130.

25. Dowell D, Haegerich T, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain -- United States, 2016. MMWR Recomm Rep. 2016;65:1-49.

26. Federation of State Medical Boards of the United States I. Model Policy on the Use of Opioid Analgesics in the Treatment of Chronic Pain. Available at: https://www.fsmb.org/Media/Default/PDF/Advocacy/Opioid%20Guidelines%20As%20Adopted%20April%202017_FINAL.pdf. Accessed October 1, 2017.

27. Federation of State Medical Boards of the United States I. Guidelines for the Chronic Use of Opioid Analgesics. Available at: https://www.fsmb.org/Media/Default/PDF/Advocacy/Opioid%20Guidelines%20As%20Adopted%20April%202017_FINAL.pdf. Accessed June 1, 2017.

28. Hauk L. Management of Chronic Pain and Opioid Misuse: A Position Paper from the AAFP. Am Fam Physician. 2017;95:458-459.

29. ICSI Patient Advisory Council. Pain: Assessment, Non-Opioid Treatment Approaches and Opioid Management Guideline (2016). Available at: https://www.icsi.org/_asset/ypv5rn/2016painsealevidence.pdf. Accessed October 1, 2017.

30. Intermountain Healthcare. Clinical Guideline: Acute Pain Opioid Prescribing Guidelines. Available at: https://intermountainphysician.org/Documents/AcutePainOpioidPrescribing_FINAL.pdf. Accessed October 1, 2017.

31. Massachusetts Medical Society. Opioid Therapy and Physician Communication Guidelines. Available at: http://www.massmed.org/opioid-guidelines/#.W43RqH4nbiw. Accessed October 1, 2017.

32. American Society of Anesthesiologists Task Force on Neuraxial Opioids. Practice guidelines for the prevention, detection, and management of respiratory depression associated with neuraxial opioid administration. Anesthesiology. 2009;110:218-230.

33. Oregon Pain Guidance Group. Oregon Acute Pain Flow Sheet for the Evaluation and Treatment of Acute Pain. Available at: https://www.oregonpainguidance.org/app/content/uploads/2016/05/Acute-and-Chronic-Pain-flow-sheets.pdf. Accessed August 22, 2018.

34. Pennsylvania Orthopaedic Society. Opioid Recommendations for Acute Pain. Available at: https://www.paorthosociety.org/resources/Documents/POS%20Opioid%20Statement%20and%20Recommendations%20Final.pdf. Accessed August 28, 2018.

35. Substance Abuse and Mental Health Services Administration. SAMHSA Opioid Overdose Prevention Toolkit. Available at: https://store.samhsa.gov/shin/content//SMA16-4742/SMA16-4742.pdf. Accessed October 1, 2017.

36. U.S. Department of Veterans Affairs. Pain Management Opioid Safety Educational Guide. Available at: https://www.va.gov/PAINMANAGEMENT/docs/OSI_1_Toolkit_Pain_Educational_Guide.pdf. Accessed October 1, 2017.

37. U.S. Department of Veterans Affairs. Pain Management Opioid Taper Decision Tool: A VA Clinician's Guide. Available at: https://www.pbm.va.gov/AcademicDetailingService/Documents/Pain_Opioid_Taper_Tool_IB_10_939_P96820.pdf. Accessed October 1, 2017.

38. Washington State Agency Medical Directors' Group. Interagency Guideline on Prescribing Opioids for Pain. Available at: http://www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf. Accessed October 1, 2017.

39. World Health Organization. Scoping Document for WHO Guidelines for the pharmacological treatment of persisting pain in adults with medical illnesses. Available at: http://www.who.int/medicines/areas/quality_safety/Scoping_WHO_GLs_PersistPainAdults_web version.pdf. Accessed October 1, 2017.

40. Menendez ME, Ring D. Factors Associated with Greater Pain Intensity. Hand Clin. 2016;32:27-31.

41. Golkari S, Teunis T, Ring D, et al. Changes in Depression, Health Anxiety, and Pain Catastrophizing Between Enrollment and 1 Month After a Radius Fracture. Psychosomatics. 2015;56:652-657.

42. Sullivan MJ, Thorn B, Haythornthwaite JA, et al. Theoretical perspectives on the relation between catastrophizing and pain. Clin J Pain. 2001;17:52-64.

43. Archer KR, Castillo RC, Wegener ST, et al. Pain and satisfaction in hospitalized trauma patients: the importance of self-efficacy and psychological distress. J Trauma Acute Care Surg. 2012;72:1068-1077.

44. Bot AG, Bekkers S, Arnstein PM, et al. Opioid use after fracture surgery correlates with pain intensity and satisfaction with pain relief. Clin Orthop Relat Res. 2014;472:2542-2549.

45. Nota SP, Spit SA, Voskuyl T, et al. Opioid Use, Satisfaction, and Pain Intensity After Orthopedic Surgery. Psychosomatics. 2015;56:479-485.

1164 46. Bot AG, Bekkers S, Herndon JH, et al. Determinants of disability after proximal
1165 interphalangeal joint sprain or dislocation. Psychosomatics. 2014;55:595-601.
1166 47. Briet JP, Houwert RM, Hageman M, et al. Factors associated with pain intensity and
1167 physical limitations after lateral ankle sprains. Injury. 2016;47:2565-2569.
1168 48. Das De S, Vranceanu AM, Ring DC. Contribution of kinesophobia and catastrophic
1169 thinking to upper-extremity-specific disability. J Bone Joint Surg Am. 2013;95:76-81.
1170 49. Farzad M, Asgari A, Dashab F, et al. Does Disability Correlate With Impairment After
1171 Hand Injury? Clin Orthop Relat Res. 2015;473:3470-3476.
1172 50. Finger A, Teunis T, Hageman MG, et al. Association Between Opioid Intake and
1173 Disability After Surgical Management of Ankle Fractures. J Am Acad Orthop Surg.
1174 2017;25:519-526.
1175 51. Kadzielski JJ, Bot AG, Ring D. The influence of job satisfaction, burnout, pain, and
1176 worker's compensation status on disability after finger injuries. J Hand Surg Am. 2012;37:1812-
1177 1819.
1178 52. Teunis T, Bot AG, Thornton ER, et al. Catastrophic Thinking Is Associated With Finger
1179 Stiffness After Distal Radius Fracture Surgery. J Orthop Trauma. 2015;29:e414-420.
1180 53. Vranceanu A, Bachoura A, Weening A, et al. Psychological factors predict disability and
1181 pain intensity after skeletal trauma. J Bone Joint Surg Am. 2014;96:e20.
1182 54. Carragee EJ, Vittum D, Truong TP, et al. Pain control and cultural norms and
1183 expectations after closed femoral shaft fractures. Am J Orthop (Belle Mead NJ). 1999;28:97-102.
1184 55. Helmerhorst GT, Lindenhovius AL, Vrahas M, et al. Satisfaction with pain relief after
1185 operative treatment of an ankle fracture. Injury. 2012;43:1958-1961.

1186 56. Helmerhorst GT, Vranceanu AM, Vrahas M, et al. Risk factors for continued opioid use
1187 one to two months after surgery for musculoskeletal trauma. J Bone Joint Surg Am.
1188 2014;96:495-499.
1189 57. Lindenhovius AL, Helmerhorst GT, Schnellen AC, et al. Differences in prescription of
1190 narcotic pain medication after operative treatment of hip and ankle fractures in the United States
1191 and The Netherlands. J Trauma. 2009;67:160-164.
1192 58. Archer KR, Abraham CM, Obremskey WT. Psychosocial Factors Predict Pain and
1193 Physical Health After Lower Extremity Trauma. Clin Orthop Relat Res. 2015;473:3519-3526.
1194 59. Archer KR, Abraham CM, Song Y, et al. Cognitive-behavioral determinants of pain and
1195 disability two years after traumatic injury: A cross-sectional survey study. J Trauma Acute Care
1196 Surg. 2012;72:473-479.
1197 60. Archer KR, Heins SE, Abraham CM, et al. Clinical Significance of Pain at Hospital
1198 Discharge Following Traumatic Orthopedic Injury: General Health, Depression, and PTSD
1199 Outcomes at 1 Year. Clin J Pain. 2016;32:196-202.
1200 61. Castillo R, MacKenzie E, Wegener S, et al. Prevalence of Chronic Pain Seven Years
1201 Following Limb Threatening Lower Extremity Trauma. Pain. 2006;124:321-329.
1202 62. Castillo R, Wegener S, Heins S, et al. Longitudinal relationships between anxiety,
1203 depression, and pain: results from a two-year cohort study of lower extremity trauma patients.
1204 Pain. 2013;154:2860-2866.
1205 63. Clay FJ, Watson WL, Newstead SV, et al. A systematic review of early prognostic
1206 factors for persisting pain following acute orthopedic trauma. Pain Res Manag. 2012;17:35-44.
1207 64. Crichlow RJ, Andres PL, Morrison SM, et al. Depression in orthopaedic trauma patients.
1208 Prevalence and severity. J Bone Joint Surg Am. 2006;88:1927-1933.

65. Edwards RR, Dworkin RH, Sullivan MD, et al. The Role of Psychosocial Processes in the Development and Maintenance of Chronic Pain. J Pain. 2016;17:T70-92.

66. Gopinath B, Jagnoor J, Nicholas M, et al. Presence and predictors of persistent pain among persons who sustained an injury in a road traffic crash. Eur J Pain. 2015;19:1111-1118.

67. Hanley MA, Jensen MP, Ehde DM, et al. Psychosocial predictors of long-term adjustment to lower-limb amputation and phantom limb pain. Disabil Rehabil. 2004;26:882-893.

68. McCarthy ML, MacKenzie EJ, Edwin D, et al. Psychological distress associated with severe lower-limb injury. J Bone Joint Surg Am. 2003;85-a:1689-1697.

69. Nota SP, Bot AG, Ring D, et al. Disability and depression after orthopaedic trauma. Injury. 2015;46:207-212.

70. Ponsford J, Hill B, Karamitsios M, et al. Factors influencing outcome after orthopedic trauma. J Trauma. 2008;64:1001-1009.

71. Schweininger S, Forbes D, Creamer M, et al. The temporal relationship between mental health and disability after injury. Depress Anxiety. 2015;32:64-71.

72. Soberg HL, Bautz-Holter E, Roise O, et al. Mental health and posttraumatic stress symptoms 2 years after severe multiple trauma: self-reported disability and psychosocial functioning. Arch Phys Med Rehabil. 2010;91:481-488.

73. van Leeuwen WF, van der Vliet QM, Janssen SJ, et al. Does perceived injustice correlate with pain intensity and disability in orthopaedic trauma patients? Injury. 2016;47:1212-1216.

74. Warren AM, Foreman ML, Bennett MM, et al. Posttraumatic stress disorder following traumatic injury at 6 months: associations with alcohol use and depression. J Trauma Acute Care Surg. 2014;76:517-522.

1231 75. Wegener S, Castillo R, Haythornthwaite J, et al. Psychological Distress Mediates the
1232 Effect of Pain on Function. Pain. 2011;152:1349-1357.
1233 76. Williams AE, Newman JT, Ozer K, et al. Posttraumatic stress disorder and depression
1234 negatively impact general health status after hand injury. J Hand Surg Am. 2009;34:515-522.
1235 77. Zatzick DF, Jurkovich GJ, Fan MY, et al. Association between posttraumatic stress and
1236 depressive symptoms and functional outcomes in adolescents followed up longitudinally after
1237 injury hospitalization. Arch Pediatr Adolesc Med. 2008;162:642-648.
1238 78. Merskey H, Bogduk N. Classification of Chronic Pain: Descriptions of Chronic Pain
1239 Syndromes and Definitions of Pain Terms. Washington, DC: IASP Press; 1994.
1240 79. Andersson AL, Dahlback LO, Bunketorp O. Psychosocial aspects of road traffic trauma--
1241 benefits of an early intervention? Injury. 2005;36:917-926.
1242 80. Berube M, Choiniere M, Laflamme YG, et al. Acute to chronic pain transition in
1243 extremity trauma: A narrative review for future preventive interventions (part 1). Int J Orthop
1244 Trauma Nurs. 2016;23:47-59.
1245 81. Berube M, Choiniere M, Laflamme YG, et al. Acute to chronic pain transition in
1246 extremity trauma: A narrative review for future preventive interventions (part 2). Int J Orthop
1247 Trauma Nurs. 2017;24:59-67.
1248 82. Berube M, Gelinas C, Martorella G, et al. A Hybrid Web-Based and In-Person Self-
1249 Management Intervention to Prevent Acute to Chronic Pain Transition After Major Lower
1250 Extremity Trauma (iPACT-E-Trauma): Protocol for a Pilot Single-Blind Randomized Controlled
1251 Trial. JMIR Res Protoc. 2017;6:e125.

1252 83. Bisson JI, Shepherd JP, Joy D, et al. Early cognitive-behavioural therapy for post-
1253 traumatic stress symptoms after physical injury. Randomised controlled trial. Br J Psychiatry.
1254 2004;184:63-69.
1255 84. Campbell L, Kenardy J, Andersen T, et al. Trauma-focused cognitive behaviour therapy
1256 and exercise for chronic whiplash: protocol of a randomised, controlled trial. J Physiother.
1257 2015;61:218.
1258 85. Castillo RC, Raja SN, Frey KP, et al. Improving Pain Management and Long-Term
1259 Outcomes Following High-Energy Orthopaedic Trauma (Pain Study). J Orthop Trauma. 2017;31
1260 Suppl 1:S71-s77.
1261 86. Chad-Friedman E, Talaei-Khoei M, Ring D, et al. First Use of a Brief 60-second
1262 Mindfulness Exercise in an Orthopedic Surgical Practice; Results from a Pilot Study. Arch Bone
1263 Jt Surg. 2017;5:400-405.
1264 87. De Silva M, Maclachlan M, Devane D, et al. Psychosocial interventions for the
1265 prevention of disability following traumatic physical injury. Cochrane Database Syst Rev.
1266 2009;10.1002/14651858.CD006422.pub3:Cd006422.
1267 88. Goudie S, Dixon D, McMillan G, et al. Is Use of a Psychological Workbook Associated
1268 With Improved Disabilities of the Arm, Shoulder and Hand Scores in Patients With Distal
1269 Radius Fracture? Clin Orthop Relat Res. 2018;476:832-845.
1270 89. Holmes A, Hodgins G, Adey S, et al. Trial of interpersonal counselling after major
1271 physical trauma. Aust N Z J Psychiatry. 2007;41:926-933.
1272 90. Pirente N, Blum C, Wortberg S, et al. Quality of life after multiple trauma: the effect of
1273 early onset psychotherapy on quality of life in trauma patients. Langenbecks Arch Surg.
1274 2007;392:739-745.

1275 91. Turpin G, Downs M, Mason S. Effectiveness of providing self-help information
1276 following acute traumatic injury: randomised controlled trial. Br J Psychiatry. 2005;187:76-82.
1277 92. Vranceanu A, Hageman M, Strooker J, et al. A preliminary RCT of a mind body skills
1278 based intervention addressing mood and coping strategies in patients with acute orthopaedic
1279 trauma. Injury. 2015;46:552-557.
1280 93. Zatzick D, Roy-Byrne P, Russo J, et al. A randomized effectiveness trial of stepped
1281 collaborative care for acutely injured trauma survivors. Arch Gen Psychiatry. 2004;61:498-506.
1282 94. Zatzick DF, Roy-Byrne P, Russo JE, et al. Collaborative interventions for physically
1283 injured trauma survivors: a pilot randomized effectiveness trial. Gen Hosp Psychiatry.
1284 2001;23:114-123.
1285 95. Ong AD, Zautra AJ, Reid MC. Psychological resilience predicts decreases in pain
1286 catastrophizing through positive emotions. Psychol Aging. 2010;25:516-523.
1287 96. Walsh MV, Armstrong TW, Poritz J, et al. Resilience, Pain Interference, and Upper Limb
1288 Loss: Testing the Mediating Effects of Positive Emotion and Activity Restriction on Distress.
1289 Arch Phys Med Rehabil. 2016;97:781-787.
1290 97. Eccleston C, Fisher E, Craig L, et al. Psychological therapies (Internet-delivered) for the
1291 management of chronic pain in adults. Cochrane Database Syst Rev.
1292 2014;10.1002/14651858.CD010152.pub2:Cd010152.
1293 98. Macea DD, Gajos K, Daglia Calil YA, et al. The efficacy of Web-based cognitive
1294 behavioral interventions for chronic pain: a systematic review and meta-analysis. J Pain.
1295 2010;11:917-929.

99. Palermo TM, Eccleston C, Lewandowski AS, et al. Randomized controlled trials of psychological therapies for management of chronic pain in children and adolescents: an updated meta-analytic review. Pain. 2010;148:387-397.

100. Bradt J, Dileo C, Potvin N. Music for stress and anxiety reduction in coronary heart disease patients. Cochrane Database Syst Rev. 2013;10.1002/14651858.CD006577.pub3:Cd006577.

101. Lee YL, Wu Y, Tsang HW, et al. A systematic review on the anxiolytic effects of aromatherapy in people with anxiety symptoms. J Altern Complement Med. 2011;17:101-108.

102. Lakhan SE, Sheafer H, Tepper D. The Effectiveness of Aromatherapy in Reducing Pain: A Systematic Review and Meta-Analysis. Pain Res Treat. 2016;2016:8158693.

103. Chou R, Gordon DB, de Leon-Casasola OA, et al. 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.

104. Bjordal J, Johnson M, Ljunggreen A. Transcutaneous electrical nerve stimulation (TENS) can reduce postoperative analgesic consumption. A meta-analysis with assessment of optimal treatment parameters for postoperative pain. Eur J Pain. 2003;7:181-188.

105. Tedesco D, Gori D, Desai KR, et al. Drug-Free Interventions to Reduce Pain or Opioid Consumption After Total Knee Arthroplasty: A Systematic Review and Meta-analysis. JAMA Surg. 2017;152:e172872.

106. Rakel BA, Zimmerman MB, Geasland K, et al. Transcutaneous electrical nerve stimulation for the control of pain during rehabilitation after total knee arthroplasty: A randomized, blinded, placebo-controlled trial. Pain. 2014;155:2599-2611.

107. Mahure SA, Rokito AS, Kwon YW. Transcutaneous electrical nerve stimulation for postoperative pain relief after arthroscopic rotator cuff repair: a prospective double-blinded randomized trial. J Shoulder Elbow Surg. 2017;26:1508-1513.

108. Hamza MA, White PF, Ahmed HE, et al. Effect of the frequency of transcutaneous electrical nerve stimulation on the postoperative opioid analgesic requirement and recovery profile. Anesthesiology. 1999;91:1232-1238.

109. Benedetti F, Amanzio M, Casadio C, et al. Control of postoperative pain by transcutaneous electrical nerve stimulation after thoracic operations. Ann Thorac Surg. 1997;63:773-776.

110. Zeng C, Li H, Yang T, et al. Electrical stimulation for pain relief in knee osteoarthritis: systematic review and network meta-analysis. Osteoarthritis Cartilage. 2015;23:189-202.

111. Deal D, Tipton J, Rosencrance E, et al. Ice reduces edema: A study of microvascular permeability in rats. J Bone Joint Surg. 2002;84-A:1573-1578.

112. Schaser KD, Stover JF, Melcher I, et al. Local cooling restores microcirculatory hemodynamics after closed soft-tissue trauma in rats. J Trauma. 2006;61:642-649.

113. Kenjo T, Kikuchi S, Konno S. Cooling decreases fos-Immunoreactivity in the rat after formalin injection. Clin Orthop Rel Res. 2002;394:271-277.

114. Schaser KD, Disch AC, Stover JF, et al. Prolonged superficial local cryotherapy attenuates microcirculatory impairment, regional inflammation, and muscle necrosis after closed soft tissue injury in rats. Am J Sports Med. 2007;35:93-102.

115. Scumpia PO, Sarcia PJ, Kelly KM, et al. Hypothermia induces anti-inflammatory cytokines and inhibits nitric oxide and myeloperoxidase-mediated damage in the hearts of endotoxemic rats. Chest. 2004;125:1483-1491.

116. Stalman A, Berglund L, Dungnerc E, et al. Temperature-sensitive release of prostaglandin E(2) and diminished energy requirements in synovial tissue with postoperative cryotherapy: a prospective randomized study after knee arthroscopy. J Bone Joint Surg Am. 2011;93:1961-1968.

117. Ho S, Coel M, Kagawa R, et al. The effects of ice on blood flow and bone metabolism in knees. Am J Sports Med. 1994;22:537-540.

118. Ho S, Illgen R, Meyer R, et al. Comparison of various icing times in decreasing bone metabolism and blood flow in the knee. Am J Sports Med. 1995;23:74-76.

119. Knobloch K, Grasemann R, Jagodzinski M, et al. Changes of Achilles midportion tendon microcirculation after repetitive simultaneous cryotherapy and compression using a Cryo/Cuff. Am J Sports Med. 2006;34:1953-1959.

120. White GE, Wells GD. Cold-water immersion and other forms of cryotherapy: physiological changes potentially affecting recovery from high-intensity exercise. Extrem Physiol Med. 2013;2:26.

121. Algafly A, George K. The effect of cryotherapy on nerve conduction velocity, pain threshold and pain tolerance. Br J Sports Med. 2007;41:365-369.

122. Adie S, Kwan A, Naylor J, et al. Cryotherapy following total knee replacement. Cochrane Database Syst Rev. 2012;10.1002/14651858.CD007911.pub2:CD007911.

123. Brandsson S, Rydgren B, Hedner T, et al. Postoperative analgesic effects of an external cooling system and intra-articular bupivacaine/morphine after arthroscopic cruciate ligament surgery. Knee Surg Sports Traumatol Arthrosc. 1996;4:200-205.

124. Kuyucu E, Bulbul M, Kara A, et al. Is cold therapy really efficient after knee arthroplasty? Ann Med Surg (Lond). 2015;4:475-478.

125. Levy A, Marmar E. The Role of Cold Compression Dressings in the Postoperative Treatment of Total Knee Arthroplasty. Clin Orthop Rel Res. 1993;297:174-178.

126. Morsi E. Continuous-flow cold therapy after total knee arthroplasty. J Arthroplasty. 2002;17:718-722.

127. Ohkoshi Y, Ohkoshi M, Nagasaki S, et al. The effect of cryotherapy on intraarticular temperature and postoperative care after anterior cruciate ligament reconstruction. Am J Sports Med. 1999;27:357-362.

128. Raynor MC, Pietrobon R, Guller U, et al. Cryotherapy after ACL reconstruction: a meta-analysis. J Knee Surg. 2005;18:123-129.

129. Saito N, Horiuchi H, Kobayashi S, et al. Continuous Local Cooling for Pain Relief Following Total Hip Arthroplasty. J Arthroplasty. 2004;19:334-337.

130. Singh H, Osbahr D, Holovacs T, et al. The efficacy of continuous cryotherapy on the postoperative shoulder: A prospective, randomized investigation. J Shoulder Elbow Surg. 2001;10:522-525.

131. Speer K, Warren R, Horowitz L. The efficacy of cryotherapy in the postoperative shoulder. J Shoulder Elbow Surg. 1996;5:62-68.

132. Webb JM, Williams D, Ivory JP, et al. The use of cold compression dressings after total knee replacement: a randomized controlled trial. Orthopedics. 1998;21:59-61.

133. Barber F, McGuire D, Click S. Continuous-flow cold therapy for outpatient anterior cruciate ligament reconstruction Arthroscopy. 1998;14:130-135.

134. Daniel DM, Stone ML, Arendt DL. The effect of cold therapy on pain, swelling, and range of motion after anterior cruciate ligament reconstructive surgery. Arthroscopy. 1994;10:530-533.

135. Gibbons C, Solan M, Ricketts D. Cryotherapy compared with Robert Jones bandage after total knee replacement: A prospective randomized trial. Int Orthop. 2001;25:250-252.

136. Kullenberg B, Ylipaa S, Soderlund K, et al. Postoperative Cryotherapy After Total Knee Arthroplasty: A Prospective Study of 86 Patients. J Arthroplasty. 2006;21:1175-1179.

137. Wittig-Wells D, Johnson I, Samms-McPherson J, et al. Does the use of a brief cryotherapy intervention with analgesic administration improve pain management after total knee arthroplasty? Orthop Nurs. 2015;34:148-153.

138. Holmstrom A, Hardin BC. Cryo/Cuff compared to epidural anesthesia after knee unicompartmental arthroplasty: a prospective, randomized and controlled study of 60 patients with a 6-week follow-up. J Arthroplasty. 2005;20:316-321.

139. Dervin GF, Taylor DE, Keene GC. Effects of cold and compression dressings on early postoperative outcomes for the arthroscopic anterior cruciate ligament reconstruction patient. J Orthop Sports Phys Ther. 1998;27:403-406.

140. Edwards DJ, Rimmer M, Keene GC. The use of cold therapy in the postoperative management of patients undergoing arthroscopic anterior cruciate ligament reconstruction. Am J Sports Med. 1996;24:193-195.

141. Walker RH, Morris BA, Angulo DL, et al. Postoperative use of continuous passive motion, transcutaneous electrical nerve stimulation, and continuous cooling pad following total knee arthroplasty. J Arthroplasty. 1991;6:151-156.

142. Bech M, Moorhen J, Cho M, et al. Device or ice: the effect of consistent cooling using a device compared with intermittent cooling using an ice bag after total knee arthroplasty. Physiother Can. 2015;67:48-55.

143. Demoulin C, Brouwers M, Darot S, et al. Comparison of gaseous cryotherapy with more traditional forms of cryotherapy following total knee arthroplasty. Ann Phys Rehabil Med. 2012;55:229-240.

144. Desteli EE, Imren Y, Aydin N. Effect of both preoperative andpostoperative cryoceutical treatment on hemostasis and postoperative pain following total knee arthroplasty. Int J Clin Exp Med. 2015;8:19150-19155.

145. Kraeutler MJ, Reynolds KA, Long C, et al. Compressive cryotherapy versus ice-a prospective, randomized study on postoperative pain in patients undergoing arthroscopic rotator cuff repair or subacromial decompression. J Shoulder Elbow Surg. 2015;24:854-859.

146. Ruffilli A, Castagnini F, Traina F, et al. Temperature-Controlled Continuous Cold Flow Device after Total Knee Arthroplasty: A Randomized Controlled Trial Study. J Knee Surg. 2017;30:675-681.

147. Smith J, Stevens J, Taylor M, et al. A randomized, controlled trial comparing compression bandaging and cold therapy in postoperative total knee replacement surgery. Orthop Nurs. 2002;21:61-66.

148. Su E, Perna M, Boettner F, et al. A prospective, multi-center, randomized trial to evaluate the efficacy of a cryopneumatic device on total knee arthroplasty recovery J Bone Joint Surg Br. 2012;94-B:153-156.

149. Thienpont E. Does advanced cryotherapy reduce pain and narcotic consumption after knee arthroplasty? . Clin Orthop Rel Res. 2014;472:3417-3423.

150. Whitelaw GP, DeMuth KA, Demos HA, et al. The use of the Cryo/Cuff versus ice and elastic wrap in the postoperative care of knee arthroscopy patients. Am J Knee Surg. 1995;8:28-30; discussion 30-21.

151. Barber FA. A comparison of crushed ice and continuous flow cold therapy. Am J Knee Surg. 2000;13:97-101; discussion 102.

152. Meyer-Marcotty M, Jungling O, Vaske B, et al. Standardized combined cryotherapy and compression using Cryo/Cuff after wrist arthroscopy. Knee Surg Sports Traumatol Arthrosc. 2011;19:314-319.

153. Schinsky M, McCune C, Bonomi J. Multifaceted Comparison of Two Cryotherapy Devices Used After Total Knee Arthroplasty: Cryotherapy Device Comparison. Orthop Nurs. 2016;35:309-316.

154. Schroder D, Passler H. Combination of cold and compression after knee surgery A prospective randomized study Knee Surg, Sports Traumatol, Arthroscopy. 1994;2:158-165.

155. Song M, Sun X, Tian X, et al. Compressive cryotherapy versus cryotherapy alone in patients undergoing knee surgery: a meta-analysis. Springerplus. 2016;5:1074.

156. Cohn B, Draeger R, Jackson D. The effects of cold therapy in the postoperative management of pain in patients undergoing anterior cruciate ligament reconstruction. Am J Sports Med. 1989;17:344-349.

1449 157. Healy W, Seidman J, Pfeifer B, et al. Cold compressive dressing after total knee
1450 arthroplasty Clin Orthop Rel Res. 1994;299:143-146.
1451 158. Konrath GA, Lock T, Goitz HT, et al. The use of cold therapy after anterior cruciate
1452 ligament reconstruction. A prospective, randomized study and literature review. Am J Sports
1453 Med. 1996;24:629-633.
1454 159. Woolf S, Barfield W, Merrill K, et al. Comparison of a continuous temperature-
1455 controlled cryotherapy device to a simple icing regimen following outpatient knee arthroscopy. .
1456 J Knee Surg. 2008;21:15-19.
1457 160. Bassett F, Kirkpatrick J, Engelhardt D, et al. Cryotherapy-induced nerve injury. Am J
1458 Sports Med. 1992;20:516-518.
1459 161. Moeller J, Monroe J, McKeag D. Cryotherapy-Induced Common Peroneal Nerve Palsy.
1460 Clin J Sport Med. 1997;7:212-216.
1461 162. Kissin I. Long-term opioid treatment of chronic nonmalignant pain: unproven efficacy
1462 and neglected safety? J Pain Res. 2013;6:513.
1463 163. Gimbel J, Ahdieh H. The efficacy and safety of oral immediate-release oxymorphone for
1464 postsurgical pain. Anesth Analg. 2004;99:1472-1477.
1465 164. Iwanicki JL, Severtson SG, McDaniel H, et al. Abuse and diversion of immediate release
1466 opioid analgesics as compared to extended release formulations in the United States. PLoS One.
1467 2016;11:e0167499.
1468 165. Fishbain DA, Cole B, Lewis J, et al. What percentage of chronic nonmalignant pain
1469 patients exposed to chronic opioid analgesic therapy develop abuse/addiction and/or aberrant
1470 drug-related behaviors? A structured evidence-based review. Pain Med. 2008;9:444-459.

166. Amabile CM, Bowman BJ. Overview of oral modified-release opioid products for the management of chronic pain. Ann Pharmacother. 2006;40:1327-1335.

167. de Beer JdV, Winemaker MJ, Donnelly GA, et al. Efficacy and safety of controlled-release oxycodone and standard therapies for postoperative pain after knee or hip replacement. Can J Surg. 2005;48:277.

168. Aqua K, Gimbel JS, Singla N, et al. Efficacy and tolerability of oxymorphone immediate release for acute postoperative pain after abdominal surgery: a randomized, double-blind, active- and placebo-controlled, parallel-group trial. Clin Ther. 2007;29:1000-1012.

169. Hale ME, Fleischmann R, Salzman R, et al. Efficacy and safety of controlled-release versus immediate-release oxycodone: randomized, double-blind evaluation in patients with chronic back pain. Clin J Pain. 1999;15:179-183.

170. Kaplan R, Parris W, Citron ML, et al. Comparison of controlled-release and immediate-release oxycodone tablets in patients with cancer pain. J Clin Oncol. 1998;16:3230-3237.

171. Wen W, Taber L, Lynch S, et al. 12-Month safety and effectiveness of once-daily hydrocodone tablets formulated with abuse-deterrent properties in patients with moderate to severe chronic pain. J Opioid Mgmt. 2015;11:339-356.

172. Singla N, Pong A, Newman K, et al. Combination oxycodone 5 mg/ibuprofen 400 mg for thetreatment of pain after abdominal or pelvic surgery in women: A randomized, double-blind, placebo-and active-controlled parallel-group study. Clin Ther. 2005;27:45-57.

173. Devarakonda K, Morton T, Margulis R, et al. Pharmacokinetics and bioavailability of oxycodone and acetaminophen following single-dose administration of MNK-795, a dual-layer biphasic IR/ER combination formulation, under fed and fasted conditions. Drug Des Devel Ther. 2014;8:1125.

1494 174. Wojahn RD, Bogunovic L, Brophy RH, et al. Opioid Consumption After Knee
1495 Arthroscopy. J Bone Joint Surg Am. 2018;100:1629-1636.
1496 175. Rodgers J, Cunningham K, Fitzgerald K, et al. Opioid consumption following outpatient
1497 upper extremity surgery. J Hand Surg. 2012;37:645-650.
1498 176. Shah A, Hayes CJ, Martin BC. Characteristics of Initial Prescription Episodes and
1499 Likelihood of Long-Term Opioid Use - United States, 2006-2015. MMWR Morb Mortal Wkly
1500 Rep. 2017;66:265-269.
1501 177. Mildh LH, Scheinin H, Kirvelä OA. The concentration-effect relationship of the
1502 respiratory depressant effects of alfentanil and fentanyl. Anesth Analg. 2001;93:939-946.
1503 178. Barrett T, Kostenbader K, Nalamachu S, et al. Safety and Tolerability of Biphasic
1504 Immediate□Release/Extended□Release Oxycodone/Acetaminophen Tablets: Analysis of 11
1505 Clinical Trials. Pain Pract. 2016;16:856-868.
1506 179. Ferrell B, Wisdom C, Wenzl C, et al. Effects of controlled-released morphine on quality
1507 of life for cancer pain. Oncol Nurs Forum; 1989:521-526.
1508 180. Jones JP. United States of America v. The Purdue Frederick Company, Inc., et al.;. In:
1509 United States District Court for the Western District of Virginia Abingdon Division, ed.
1510 1:07CR0029; 2007.
1511 181. Manchikanti L, Manchukonda R, Pampati V, et al. Evaluation of abuse of prescription
1512 and illicit drugs in chronic pain patients receiving short-acting (hydrocodone) or long-acting
1513 (methadone) opioids. Pain Physician. 2005;8:257-261.
1514 182. Morton T, Kostenbader K, Montgomery J, et al. Comparison of subjective effects of
1515 extended-release versus immediate-release oxycodone/acetaminophen tablets in healthy

nondependent recreational users of prescription opioids: a randomized trial. Postgrad Med. 2014;126:20-32.

183. Park TW, Saitz R, Ganoczy D, et al. Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study. BMJ. 2015;350:h2698.

184. Wick EC, Grant MC, Wu CL. Postoperative Multimodal Analgesia Pain Management With Nonopioid Analgesics and Techniques: A Review. JAMA Surg. 2017;152:691-697.

185. Richman JM, Liu SS, Courpas G, et al. Does continuous peripheral nerve block provide superior pain control to opioids? A meta-analysis. Anesth Analg. 2006;102:248-257.

186. Rafiq S, Steinbruchel DA, Wanscher MJ, et al. Multimodal analgesia versus traditional opiate based analgesia after cardiac surgery, a randomized controlled trial. J Cardiothorac Surg. 2014;9:52.

187. Rasmussen ML, Mathiesen O, Dierking G, et al. Multimodal analgesia with gabapentin, ketamine and dexamethasone in combination with paracetamol and ketorolac after hip arthroplasty: a preliminary study. Eur J Anaesthesiol. 2010;27:324-330.

188. YaDeau JT, Brummett CM, Mayman DJ, et al. Duloxetine and Subacute Pain after Knee Arthroplasty when Added to a Multimodal Analgesic Regimen: A Randomized, Placebo-controlled, Triple-blinded Trial. Anesthesiology. 2016;125:561-572.

189. Chisholm MF, Cheng J, Fields KG, et al. Perineural dexamethasone with subsartorial saphenous nerve blocks in ACL reconstruction. Knee Surg Sports Traumatol Arthrosc. 2016:13.

190. Duncan CM, Hall Long K, Warner DO, et al. The economic implications of a multimodal analgesic regimen for patients undergoing major orthopedic surgery: a comparative study of direct costs. Reg Anesth Pain Med. 2009;34:301-307.

191. Maiese BA, Pham AT, Shah MV, et al. Hospitalization Costs for Patients Undergoing Orthopedic Surgery Treated With Intravenous Acetaminophen (IV-APAP) Plus Other IV Analgesics or IV Opioid Monotherapy for Postoperative Pain. Adv Ther. 2017;34:421-435.

192. Michelson JD, Addante RA, Charlson MD. Multimodal analgesia therapy reduces length of hospitalization in patients undergoing fusions of the ankle and hindfoot. Foot Ankle Int. 2013;34:1526-1534.

193. Fredrickson Fanzca MJ, Danesh-Clough TK, White R. Adjuvant dexamethasone for bupivacaine sciatic and ankle blocks: results from 2 randomized placebo-controlled trials. Reg Anesth Pain Med. 2013;38:300-307.

194. Mathiesen O, Dahl B, Thomsen BA, et al. A comprehensive multimodal pain treatment reduces opioid consumption after multilevel spine surgery. Eur Spine J. 2013;22:2089-2096.

195. Kim SI, Ha KY, Oh IS. Preemptive multimodal analgesia for postoperative pain management after lumbar fusion surgery: a randomized controlled trial. Eur Spine J. 2016;25:1614-1619.

196. Kang H, Ha YC, Kim JY, et al. Effectiveness of multimodal pain management after bipolar hemiarthroplasty for hip fracture: a randomized, controlled study. J Bone Joint Surg Am. 2013;95:291-296.

197. Koehler D, Marsh JL, Karam M, et al. Efficacy of Surgical-Site, Multimodal Drug Injection Following Operative Management of Femoral Fractures: A Randomized Controlled Trial. J Bone Joint Surg Am. 2017;99:512-519.

198. Lee SK, Lee JW, Choy WS. Is multimodal analgesia as effective as postoperative patient-controlled analgesia following upper extremity surgery? Orthop Traumatol Surg Res. 2013;99:895-901.

199. Zare MA, Ghalyaie AH, Fathi M, et al. Oral oxycodone plus intravenous acetaminophen versus intravenous morphine sulfate in acute bone fracture pain control: a double-blind placebo-controlled randomized clinical trial. Eur J Orthop Surg Traumatol. 2014;24:1305-1309.

200. Grumbine N, Dobrowolski C, Bernstein A. Retrospective evaluation of postoperative intralesional steroid injections on wound healing. J Foot Ankle Surg. 1998;37:135-144.

201. De Oliveira GS, Almeida MD, Benzon HT, et al. Perioperative Single Dose Systemic Dexamethasone for Postoperative PainA Meta-analysis of Randomized Controlled Trials. Anesthesiology. 2011;115:575-588.

202. Vargas III JH, Ross DG. Corticosteroids and anterior cruciate ligament repair. Am J Sports Med. 1989;17:532-534.

203. Aasboe V, Raeder JC, Groegaard B. Betamethasone reduces postoperative pain and nausea after ambulatory surgery. Anesth Analg. 1998;87:319-323.

204. Glasser RS, Knego RS, Delashaw JB, et al. The perioperative use of corticosteroids and bupivacaine in the management of lumbar disc disease. J Neurosurg. 1993;78:383-387.

205. Karst M, Kegel T, Lukas A, et al. Effect of celecoxib and dexamethasone on postoperative pain after lumbar disc surgery. Neurosurgery. 2003;53:331-337.

206. Waldron N, Jones C, Gan T, et al. Impact of perioperative dexamethasone on postoperative analgesia and side-effects: systematic review and meta-analysis. Br J Anaesth. 2012;110:191-200.

207. Curda G. Postoperative analgesic effects of dexamethasone sodium phosphate in bunion surgery. J Foot Surg. 1983;22:187-191.

208. Coluzzi F, Mattia C, Savoia G, et al. Postoperative pain surverys in Italy from 2006 and 2012: (POPSI and POPSI-2). Eur Rev Med Pharmacol Sci. 2015;19:4261-4269.

209. van Boekel LC, Brouwers EP, van Weeghel J, et al. Stigma among health professionals towards patients with substance use disorders and its consequences for healthcare delivery: systematic review. Drug Alcohol Depend. 2013;131:23-35.

210. McCaffery M, Grimm MA, Pasero C, et al. On the meaning of "drug seeking.". Pain Manag Nurs. 2005;6:122-136.

211. Compton P, Charuvastra C, Kintaudi K, et al. Pain responses in methadone-maintained opioid abusers. J Pain Symptom Manage. 2000;20:237-245.

212. Substance Abuse and Mental Health Services Administration. Results from the 2010 national survey on drug use and health: Summary of national findings. NSDUH Series H-41.2011. US Department of Health and Human Services. Rockville, MD.

213. Holman JE, Stoddard GJ, Higgins TF. Rates of prescription opiate use before and after injury in patients with orthopaedic trauma and the risk factors for prolonged opiate use. J Bone Joint Surg Am. 2013;95:1075-1080.

214. Morris BJ, Zumsteg JW, Archer KR, et al. Narcotic Use and Postoperative Doctor Shopping in the Orthopaedic Trauma Population. J Bone Joint Surg Am. 2014;96:1257-1262.

215. Coluzzi F, Bifulco F, Cuomo A, et al. The challenge of perioperative pain management in opioid-tolerant patients. Ther Clin Risk Manag. 2017;13:1163-1173.

216. Kantor TG, Cantor R, Tom E. A study of hospitalized surgical patients on methadone maintenance. Drug Alcohol Depend. 1980;6:163-173.

217. Mao J. Opioid-induced abnormal pain sensitivity: Implications in clinical opioid therapy. Pain. 2002;100:213-217.

218. Chapman RC, Donaldson G, Davis J, et al. Postoperative pain patterns in chronic patin patients: A pilot study. Pain Med. 2009;10:481-487.

1608 219. Roeckel LA, Le Coz GM, Gaveriauz-Ruff C, et al. Opioid-induced hyperalgesia: cellular
1609 and molecular mechanisms. Neuroscience. 2016;338:160-182.
1610 220. Richebe P, Beaulieu P. Perioperative pain management in the patient treated with
1611 opioids: Continuing professional development. Can J Anesthesiol. 2009;56:969-981.
1612 221. Frolich MA, Giannotti A, Modell JH. Opioid overdose in a patient using a fentanyl patch
1613 during treatment with a warming blanket. Anesthesia 2001;93:647-648.
1614 222. McCance-Katz EF, Sullivan LE, Nallani S. Drug interactions of clinical importance
1615 among the opioids, methadone and buprenorphine and other frequently presecribed medications:
1616 A review. American Journal of Addiction. 2010;19:4-16.
1617 223. J.W. C, Arnold RM. Treatment of pain in patients taking Buprenorphine for opioid
1618 addicition #221. 2012;15:613-614.
1619 224. Gervirtz C, Frost E, Bryson E. Perioperative implications od Buprenorphine maintenance
1620 treatment for opioid addicition. Anesthesia Clinics. 2011;49:147-155.
1621 225. Vadivelu N MS, Kaye AD, Urman RD. Perioperative analgesia and challenges in the
1622 drug- addicted and drug-dependent patient. Best Practices and Research in Clinical
1623 Anaesthesiology. 2014;28:91-101.
1624 226. Dean RL, Todtenkopf MS, Deaver DR, et al. Overriding the blockade of antinociceptive
1625 actions of opioids in rats treated with extended release naltrexone. Pharmacol Biochem Behav.
1626 2008;89:515-522.
1627 227. Borgeat A, Ofner C, Saporito A, et al. The effect of nonsteroidal anti-inflammatory drugs
1628 on bone healing in humans: A qualitative, systematic review. J Clin Anesth. 2018;49:92-100.
1629 228. Dodwell ER, Latorre JG, Parisini E, et al. NSAID exposure and risk of nonunion: a meta-
1630 analysis of case-control and cohort studies. Calcif Tissue Int. 2010;87:193-202.

229. Kurmis AP, Kurmis TP, O'Brien JX, et al. The effect of nonsteroidal anti-inflammatory drug administration on acute phase fracture-healing: a review. J Bone Joint Surg Am. 2012;94:815-823.

230. Geusens P, Emans PJ, de Jong JJ, et al. NSAIDs and fracture healing. Curr Opin Rheumatol. 2013;25:524-531.

231. Dahners LE, Mullis BH. Effects of nonsteroidal anti-inflammatory drugs on bone formation and soft-tissue healing. J Am Acad Orthop Surg. 2004;12:139-143.

232. Murnaghan M, Li G, Marsh DR. Nonsteroidal anti-inflammatory drug-induced fracture nonunion: an inhibition of angiogenesis? J Bone Joint Surg Am. 2006;88 Suppl 3:140-147.

233. Brown KM, Saunders MM, Kirsch T, et al. Effect of COX-2-specific inhibition on fracture-healing in the rat femur. J Bone Joint Surg Am. 2004;86-a:116-123.

234. Giannoudis PV, MacDonald DA, Matthews SJ, et al. Nonunion of the femoral diaphysis. The influence of reaming and non-steroidal anti-inflammatory drugs. J Bone Joint Surg Br. 2000;82:655-658.

235. Bhattacharyya T, Levin R, Vrahas MS, et al. Nonsteroidal antiinflammatory drugs and nonunion of humeral shaft fractures. Arthritis Rheum. 2005;53:364-367.

236. Jeffcoach DR, Sams VG, Lawson CM, et al. Nonsteroidal anti-inflammatory drugs' impact on nonunion and infection rates in long-bone fractures. J Trauma Acute Care Surg. 2014;76:779-783.

237. Sagi HC, Jordan CJ, Barei DP, et al. Indomethacin prophylaxis for heterotopic ossification after acetabular fracture surgery increases the risk for nonunion of the posterior wall. J Orthop Trauma. 2014;28:377-383.

1653 238. Marquez-Lara A, Hutchinson ID, Nunez F, Jr., et al. Nonsteroidal Anti-Inflammatory
1654 Drugs and Bone-Healing: A Systematic Review of Research Quality. JBJS Rev. 2016;4:doi:
1655 10.2106/JBJS.RVW.O.00055.
1656 239. Perez-Castrillon JL, Olmos JM, Gomez JJ, et al. Expression of opioid receptors in
1657 osteoblast-like MG-63 cells, and effects of different opioid agonists on alkaline phosphatase and
1658 osteocalcin secretion by these cells. Neuroendocrinology. 2000;72:187-194.
1659 240. Chrastil J, Sampson C, Jones KB, et al. Postoperative opioid administration inhibits bone
1660 healing in an animal model. Clin Orthop Relat Res. 2013;471:4076-4081.
1661 241. Smith HS, Elliott JA. Opioid-induced androgen deficiency (OPIAD). Pain Physician.
1662 2012;15:ES145-156.
1663 242. Brinker MR, O'Connor DP, Monla YT, et al. Metabolic and endocrine abnormalities in
1664 patients with nonunions. J Orthop Trauma. 2007;21:557-570.
1665 243. Chrastil J, Sampson C, Jones KB, et al. Evaluating the affect and reversibility of opioid-
1666 induced androgen deficiency in an orthopaedic animal fracture model. Clin Orthop Relat Res.
1667 2014;472:1964-1971.
1668 244. Poonai N, Bhullar G, Lin K, et al. Oral administration of morphine versus ibuprofen to
1669 manage postfracture pain in children: a randomized trial. CMAJ. 2014;186:1358-1363.
1670 245. Beaudoin FL, Gutman R, Merchant RC, et al. Persistent pain after motor vehicle
1671 collision: comparative effectiveness of opioids vs nonsteroidal antiinflammatory drugs
1672 prescribed from the emergency department-a propensity matched analysis. Pain. 2017;158:289-
1673 295.
1674 246. Pollack CV, Jr., Diercks DB, Thomas SH, et al. Patient-reported Outcomes from A
1675 National, Prospective, Observational Study of Emergency Department Acute Pain Management

With an Intranasal Nonsteroidal Anti-inflammatory Drug, Opioids, or Both. Acad Emerg Med. 2016;23:331-341.

247. Ong CK, Seymour RA, Lirk P, et al. Combining paracetamol (acetaminophen) with nonsteroidal antiinflammatory drugs: a qualitative systematic review of analgesic efficacy for acute postoperative pain. Anesth Analg. 2010;110:1170-1179.

248. Beaudoin FL, Haran JP, Liebmann O. A comparison of ultrasound-guided three-in-one femoral nerve block versus parenteral opioids alone for analgesia in emergency department patients with hip fractures: a randomized controlled trial. Acad Emerg Med. 2013;20:584-591.

249. Beaudoin FL, Nagdev A, Merchant RC, et al. Ultrasound-guided femoral nerve blocks in elderly patients with hip fractures. Am J Emerg Med. 2010;28:76-81.

250. Brisbane Orthopaedic & Sports Medicine Centre Writing Committee, McMeniman TJ, McMeniman PJ, et al. Femoral nerve block vs fascia iliaca block for total knee arthroplasty postoperative pain control: a prospective, randomized controlled trial. J Arthroplasty. 2010;25:1246-1249.

251. Fletcher AK, Rigby AS, Heyes FL. Three-in-one femoral nerve block as analgesia for fractured neck of femur in the emergency department: a randomized, controlled trial. Ann Emerg Med. 2003;41:227-233.

252. Foss NB, Kristensen BB, Bundgaard M, et al. Fascia iliaca compartment blockade for acute pain control in hip fracture patients: a randomized, placebo-controlled trial. Anesthesiology. 2007;106:773-778.

253. Godoy-Monzon D, Vazquez J, Jauregui JR, et al. Pain treatment in post-traumatic hip fracture in the elderly: regional block vs. systemic non-steroidal analgesics. Int J Emerg Med. 2010;3:321-325.

254. Haddad FS, Williams RL. Femoral nerve block in extracapsular femoral neck fractures. J Bone Joint Surg Br. 1995;77:922-923.

255. Haines L, Dickman E, Ayvazyan S, et al. Ultrasound-guided fascia iliaca compartment block for hip fractures in the emergency department. J Emerg Med. 2012;43:692-697.

256. Morrison RS, Dickman E, Hwang U, et al. Regional Nerve Blocks Improve Pain and Functional Outcomes in Hip Fracture: A Randomized Controlled Trial. J Am Geriatr Soc. 2016;64:2433-2439.

257. Mouzopoulos G, Vasiliadis G, Lasanianos N, et al. Fascia iliaca block prophylaxis for hip fracture patients at risk for delirium: a randomized placebo-controlled study. J Orthop Traumatol. 2009;10:127-133.

258. Yun MJ, Kim YH, Han MK, et al. Analgesia before a spinal block for femoral neck fracture: fascia iliaca compartment block. Acta Anaesthesiol Scand. 2009;53:1282-1287.

259. Beaupre LA, Johnston DB, Dieleman S, et al. Impact of a preemptive multimodal analgesia plus femoral nerve blockade protocol on rehabilitation, hospital length of stay, and postoperative analgesia after primary total knee arthroplasty: a controlled clinical pilot study. ScientificWorldJournal. 2012;2012:273821.

260. YaDeau JT, Cahill JB, Zawadsky MW, et al. The effects of femoral nerve blockade in conjunction with epidural analgesia after total knee arthroplasty. Anesth Analg. 2005;101:891-895, table of contents.

261. Divella M, Cecconi M, Fasano N, et al. Pain relief after total hip replacement: oral CR oxycodone plus IV paracetamol versus epidural levobupivacaine and sufentanil. A randomized controlled trial. Minerva Anesthesiol. 2012;78:534-541.

262. Harsten A, Hjartarson H, Werner MU, et al. General anaesthesia with multimodal principles versus intrathecal analgesia with conventional principles in total knee arthroplasty: a consecutive, randomized study. J Clin Med Res. 2013;5:42-48.

263. Lamplot JD, Wagner ER, Manning DW. Multimodal pain management in total knee arthroplasty: a prospective randomized controlled trial. J Arthroplasty. 2014;29:329-334.

264. Moucha CS, Weiser MC, Levin EJ. Current Strategies in Anesthesia and Analgesia for Total Knee Arthroplasty. J Am Acad Orthop Surg. 2016;24:60-73.

265. Amundson AW, Johnson RL, Abdel MP, et al. A Three-arm Randomized Clinical Trial Comparing Continuous Femoral Plus Single-injection Sciatic Peripheral Nerve Blocks versus Periarticular Injection with Ropivacaine or Liposomal Bupivacaine for Patients Undergoing Total Knee Arthroplasty. Anesthesiology. 2017;126:1139-1150.

266. Ng FY, Ng JK, Chiu KY, et al. Multimodal periarticular injection vs continuous femoral nerve block after total knee arthroplasty: a prospective, crossover, randomized clinical trial. J Arthroplasty. 2012;27:1234-1238.

267. Jules-Elysee KM, Goon AK, Westrich GH, et al. Patient-controlled epidural analgesia or multimodal pain regimen with periarticular injection after total hip arthroplasty: a randomized, double-blind, placebo-controlled study. J Bone Joint Surg Am. 2015;97:789-798.

268. Barrington JW, Emerson RH, Lovald ST, et al. No Difference in Early Analgesia Between Liposomal Bupivacaine Injection and Intrathecal Morphine After TKA. Clin Orthop Relat Res. 2017;475:94-105.

269. Kelley TC, Adams MJ, Mulliken BD, et al. Efficacy of multimodal perioperative analgesia protocol with periarticular medication injection in total knee arthroplasty: a randomized, double-blinded study. J Arthroplasty. 2013;28:1274-1277.

1744 270. Xing JG, Abdallah FW, Brull R, et al. Preoperative Femoral Nerve Block for Hip
1745 Arthroscopy: A Randomized, Triple-Masked Controlled Trial. Am J Sports Med. 2015;43:2680-
1746 2687.
1747 271. Luiten WE, Schepers T, Luitse JS, et al. Comparison of continuous nerve block versus
1748 patient-controlled analgesia for postoperative pain and outcome after talar and calcaneal
1749 fractures. Foot Ankle Int. 2014;35:1116-1121.
1750 272. Schipper ON, Hunt KJ, Anderson RB, et al. Ankle Block vs Single-Shot Popliteal Fossa
1751 Block as Primary Anesthesia for Forefoot Operative Procedures: Prospective, Randomized
1752 Comparison. Foot Ankle Int. 2017;38:1188-1191.
1753 273. Galos DK, Taormina DP, Crespo A, et al. Does Brachial Plexus Blockade Result in
1754 Improved Pain Scores After Distal Radius Fracture Fixation? A Randomized Trial. Clin Orthop
1755 Relat Res. 2016;474:1247-1254.
1756 274. Goldstein RY, Montero N, Jain SK, et al. Efficacy of popliteal block in postoperative
1757 pain control after ankle fracture fixation: a prospective randomized study. J Orthop Trauma.
1758 2012;26:557-561.
1759 275. Ding DY, Manoli A, 3rd, Galos DK, et al. Continuous Popliteal Sciatic Nerve Block
1760 Versus Single Injection Nerve Block for Ankle Fracture Surgery: A Prospective Randomized
1761 Comparative Trial. J Orthop Trauma. 2015;29:393-398.
1762 276. Hunt KJ, Higgins TF, Carlston CV, et al. Continuous peripheral nerve blockade as
1763 postoperative analgesia for open treatment of calcaneal fractures. J Orthop Trauma.
1764 2010;24:148-155.
1765 277. The Joint Commission. New and revised pain assessment and management standards.
1766 Perspectives (Montclair). 2018;38:17-18.

278. The Joint Commission. Safe use of opioids in hospitals. Sentinel Event Alert. 2012;49:1-5.

279. Cashman J, Dolin S. Respiratory and haemodynamic effects of acute postoperative pain management: Evidence from published data. Br J Anaesth. 2004;93:212-223.

280. Lee L, Caplan R, Stephens L, et al. Postoperative opioid-induced respiratory depression: A closed claims analysis. Pain Med. 2015;122:659-665.

281. Jungquist CR, Willens JS, Dunwoody DR, et al. Monitoring for opioid-induced advancing sedation and respiratory depression: ASPMN membership survey of current practice. Pain Manag Nurs. 2014;15:682-693.

282. Pasero C. Assessment of Sedation During Opioid Administration for Pain Management. J Perianesth Nurs. 2009;24:186-190.

283. Nisbet AT, Mooney-Cotter F. Comparison of selected sedation scales for reporting opioid-induced sedation assessment. Pain Manag Nurs. 2009;10:154-164.

284. Pasero C. The perianesthesia nurse's role in the prevention of opioid-related sentinel events. J Perianesth Nurs. 2013;28:31-37.

285. Coffin P, Sullivan S. Cost-effectiveness of distributing naloxone to heroin users for lay overdose reversal. Ann Intern Med. 2013;158:1-9.

286. Rowe C, Santos GM, Vittinghoff E, et al. Predictors of participant engagement and naloxone utilization in a community-based naloxone distribution program. Addiction. 2015;110:1301-1310.

287. Walley A, Xuan Z, Hackman H, et al. Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis. BMJ. 2013;346:F174.

1790 288. Clark A, Wilder C, Winstanley E. A Systematic Review of Community Opioid
1791 OverdosePrevention and Naloxone Distribution Programs. J Addict Med. 2014;8:153-163.
1792 289. Finley EP, Garcia A, Rosen K, et al. Evaluating the impact of prescription drug
1793 monitoring program implementation: a scoping review. BMC Health Serv Res. 2017;17:420.
1794 290. Gugelmann H, Perrone J, Nelson L. Windmills and pill mills: can PDMPs tilt the
1795 prescription drug epidemic? . J Med Toxicol. 2012;8:378-386.
1796 291. Worley J. Prescription drug monitoring programs, a response to doctor shopping:
1797 purpose, effectiveness, and directions for future research. Issues Ment Health Nurs. 2012;33:319-
1798 328.
1799 292. Haegerich T, Paulozzi L, Manns B, et al. What we know, and don't know, about the
1800 impact of state policy and systems-level interventions on prescription drug overdose. Drug
1801 Alcohol Depend. 2014;145:34-47.
1802 293. Delcher C, Wagenaar AC, Goldberger BA, et al. Abrupt decline in oxycodone-caused
1803 mortality after implementation of Florida's Prescription Drug Monitoring Program. Drug Alcohol
1804 Depend. 2015;150:63-68.
1805 294. Nam Y, Shea D, Shi Y, et al. State Prescription Drug Monitoring Programs and Fatal
1806 Drug Overdoses. Am J Manag Care. 2017;23:297-303.
1807 295. Brown R, Riley MR, Ulrich L, et al. Impact of New York prescription drug monitoring
1808 program, I-STOP, on statewide overdose morbidity. Drug Alcohol Depend. 2017;178:348-354.
1809 296. McAllister MW, Aaronson P, Spillane J, et al. Impact of prescription drug-monitoring
1810 program on controlled substance prescribing in the ED. Am J Emerg Med. 2015;33:781-785.

297. Lin HC, Wang Z, Boyd C, et al. Associations between statewide prescription drug monitoring program (PDMP) requirement and physician patterns of prescribing opioid analgesics for patients with non-cancer chronic pain. Addict Behav. 2018;76:348-354.

298. Deyo RA, Hallvik SE, Hildebran C, et al. Association of Prescription Drug Monitoring Program Use with Opioid Prescribing and Health Outcomes: a Comparison of Program Users and Non-Users. J Pain. 2017;19:166-177.

299. Wen H, Schackman BR, Aden B, et al. States With Prescription Drug Monitoring Mandates Saw A Reduction In Opioids Prescribed To Medicaid Enrollees. Health Aff (Millwood). 2017;36:733-741.

300. Moyo P, Simoni-Wastila L, Griffin BA, et al. Impact of prescription drug monitoring programs (PDMPs) on opioid utilization among Medicare beneficiaries in 10 US States. Addiction. 2017;112:1784-1796.

301. Young LD, Kreiner PW, Panas L. Unsolicited Reporting to Prescribers of Opioid Analgesics by a State Prescription Drug Monitoring Program: An Observational Study with Matched Comparison Group. Pain Med. 2017;19:1396-1407.

302. Yarbrough CR. Prescription Drug Monitoring Programs Produce a Limited Impact on Painkiller Prescribing in Medicare Part D. Health Serv Res. 2017;53:671-689.

303. Pardo B. Do more robust prescription drug monitoring programs reduce prescription opioid overdose? Addiction. 2017;112:1773-1783.

304. Yanni LM, McKinney-Ketchum JL, Harrington SB, et al. Preparation, confidence, and attitudes about chronic noncancer pain in graduate medical education. J Grad Med Educ. 2010;2:260-268.

1833 305. Mezei L, Murinson BB, Johns Hopkins Pain Curriculum Development T. Pain education
1834 in North American medical schools. J Pain. 2011;12:1199-1208.
1835 306. Davis C, Carr D. Physician continuing education to reduce opioid misuse, abuse, and
1836 overdose: Many opportunities, few requirements. Drug Alcohol Depend. 2016;163:100-107.
1837 307. Cervero R, Gaines J. The Impact of CME on Physician Performance and Patient Health
1838 Outcomes: An Updated Synthesis of Systematic Reviews. J Contin Educ Health Prof.
1839 2015;35:131-138.
1840 308. Katzman J, Comerci G, Landen MG, et al. Rules and values: a coordinated regulatory and
1841 educational approach to the public health crises of chronic pain and addiction. Am J Public
1842 Health. 2014;104:1356-1362.
1843 309. Trudeau KJ, Hildebrand C, Garg P, et al. A Randomized Controlled Trial of the Effects
1844 of Online Pain Management Education on Primary Care Providers. Pain Med. 2017;18:680-692.
1845 310. Behar E, Rowe C, Santos G, et al. Academic Detailing Pilot for Naloxone Prescribing
1846 Among Primary Care Providers in San Francisco. Fam Med. 2017;49:122-126.
1847 311. Kattan J, Tuazon E, Paone D, et al. Public Health Detailing-A Successful Strategy to
1848 Promote Judicious Opioid Analgesic Prescribing. Am J Public Health. 2016;106:1430-1438.
1849 312. Donaldson SR, Harding AM, Taylor SE, et al. Evaluation of a targeted prescriber
1850 education intervention on emergency department discharge oxycodone prescribing. Emerg Med
1851 Australia. 2017;29:400-406.
1852 313. Hill M, Stucke R, McMahon M, et al. An Educational Intervention Decreases Opioid
1853 Prescribing After General Surgical Operations. Ann Surg. 2017;267:468-472.

314. Osborn S, Yu J, Williams B, et al. Changes in Provider Prescribing Patterns After Implementation of an Emergency Department Prescription Opioid Policy. J Emerg Med. 2017;52:538-546.

315. Zisblatt L, Hayes SM, Lazure P, et al. Safe and competent opioid prescribing education: Increasing dissemination with a train-the-trainer program. Subst Abus. 2017;38:168-176.

316. Brooks M. 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.

317. Gottlieb S. FDA Takes Important Steps to Stem the Tide of Opioid Misuse and Abuse. U.S. Food and Drug Administration; 2017.

318. Alford D, Zisblatt L, Ng P, et al. SCOPE of Pain: An Evaluation of an Opioid Risk Evaluation and Mitigation Strategy Continuing Education Program. Pain Med. 2015;17:52-63.

319. Davis D. CME and the pharmaceutical industry: two worlds, three views, four steps. CMAJ. 2004;171:149-150.

320. de la Cruz M, Reddy A, Balankari V, et al. The Impact of an Educational Program on Patient Practices for Safe Use, Storage, and Disposal of Opioids at a Comprehensive Cancer Center. Oncologist. 2017;22:115-121.

321. Rose P, Sakai J, Argue R, et al. Opioid information pamphlet increases postoperative opioid disposal rates: a before versus after quality improvement study. Can J Anesth/J Can Anesth. 2016;63:31-37.

322. McCarthy DM, Wolf MS, McConnell R, et al. Improving patient knowledge and safe use of opioids: a randomized controlled trial. Acad Emerg Med. 2015;22:331-339.

323. McCauley JL, Back SE, Brady KT. Pilot of a brief, web-based educational intervention targeting safe storage and disposal of prescription opioids. Addict Behav. 2013;38:2230-2235.

1877 324. Hero JO, McMurtry C, Benson J, et al. Discussing Opioid Risks With Patients to Reduce
1878 Misuse and Abuse: Evidence From 2 Surveys. Ann Fam Med. 2016;14:575-577.
1879 325. Waszak D, Mitchell A, Ren D, et al. A Quality Improvement Project to Improve
1880 Education Provided by Nurses to ED Patients Prescribed Opioid Analgesics at Discharge. J
1881 Emerg Nurs. 2017;44:336-344.
1882 326. Rathlev N, Almomen R, Deutsch A, et al. Randomized Controlled Trial of Electronic
1883 Care Plan Alerts and Resource Utilization by High Frequency Emergency Department Users
1884 with Opioid Use Disorder. West J Emerg Med. 2016;17:28-34.
1885 327. Butler SF, Zacharoff KL, Charity S, et al. Impact of an Electronic Pain and Opioid Risk
1886 Assessment Program: Are There Improvements in Patient Encounters and Clinic Notes? Pain
1887 Med. 2016;17:2047-2060.
1888 328. Gugelmann H, Shofer FS, Meisel ZF, et al. Multidisciplinary intervention decreases the
1889 use of opioid medication discharge packs from 2 urban EDs. Am J Emerg Med. 2013;31:1343-
1890 1348.
1891 329. Johnson JA, Woychek A, Vaughan D, et al. Screening for at-risk alcohol use and drug
1892 use in an emergency department: integration of screening questions into electronic triage forms
1893 achieves high screening rates. Ann Emerg Med. 2013;62:262-266.
1894 330. Kahler ZP, Musey PI, Schaffer JT, et al. Effect Of A "No Superuser Opioid Prescription"
1895 Policy On ED Visits And Statewide Opioid Prescription. West J Emerg Med. 2017;18:894-902.
1896 331. Zwank MD, Kennedy SM, Stuck LH, et al. Removing default dispense quantity from
1897 opioid prescriptions in the electronic medical record. Am J Emerg Med. 2017;35:1567-1569.
1898 332. Anderson D, Zlateva I, Khatri K, et al. Using health information technology to improve
1899 adherence to opioid prescribing guidelines in primary care. Clin J Pain. 2015;31:573-579.

333. Butler SF, Zacharoff K, Charity S, et al. Electronic opioid risk assessment program for chronic pain patients: barriers and benefits of implementation. Pain Pract. 2014;14:E98-e105.

334. Canada R, DiRocco D, Day S. A better approach to opioid prescribing in primary care. J Fam Pract. 2014;63:E1-E8.

335. Stanek J, Renslow M, Kalliainen L. The effect of an educational program on opioid prescription patterns in hand surgery: a quality improvement program. J Hand Surg Am. 2015;40:341-346.

336. Prabhu M, McQuaid-Hanson E, Hopp S, et al. A Shared Decision-Making Intervention to Guide Opioid Prescribing After Cesarean Delivery. Obstet Gynecol. 2017;130:42-46.

337. Mack K, Jones C, Ballesteros M. Illicit Drug Use, Illicit Drug Use Disorders, and Drug Overdose Deaths in Metropolitan and Nonmetropolitan Areas - United States. MMWR Surveill Summ. 2017;66:1-12.

338. Lin LA, Bohnert ASB, Kerns RD, et al. Impact of the Opioid Safety Initiative on opioid-related prescribing in veterans. Pain. 2017;158:833-839.

339. Losby J, Hyatt J, Kanter M, et al. Safer and more appropriate opioid prescribing: a large healthcare system's comprehensive approach. J Eval Clin Pract. 2017:1-7.

340. Akce M, Suneja A, Genord C, et al. A multifactorial intervention for hospital opioid management. J Opioid Manag. 2014;10:337-344.

341. Koopman R, Kochendorfer K, Moore J, et al. A Diabetes Dashboard and Physician Efficiency and Accuracy in Accessing Data Needed for High-Quality Diabetes Care. Ann Fam Med. 2011;9:398-405.

342. Weiner J, Balijepally V, Tanniru M. Integrating Strategic and Operational Decision Making Using Data-Driven Dashboards: The Case of St. Joseph Mercy Oakland Hospital. J Healthc Manag. 2015;60:319-330.

343. Webster L, Webster R. Predicting Aberrant Behaviors in Opioid-Treated Patients: Preliminary Validation of the Opioid Risk Tool. Pain Med. 2005;6:432-442.

344. Butler SF, Budman S, Fernandez K, et al. Cross-Validation of a Screener to Predict Opioid Misuse in Chronic Pain Patients (SOAPP-R). J Addict Med. 2009;3:66-73.

345. Yudko E, Lozhkina O, Fouts A. A comprehensive review of the psychometric properties of the Drug Abuse Screening Test. J Subst Abuse Treat. 2007;32:189-198.

346. Jones T, Lookatch S, Grant P, et al. Further validation of an opioid risk assessment tool: the Brief Risk Interview. J Opioid Manag. 2014;10:353-364.

347. Butler SF, Budman S, Fernandez K, et al. Development and validation of the Current Opioid Misuse Measure. Pain. 2007;130:144-156.

348. Dowell D, Zhang K, Noonan RK, et al. Mandatory Provider Review And Pain Clinic Laws Reduce The Amounts Of Opioids Prescribed And Overdose Death Rates. Health Aff (Millwood). 2016;35:1876-1883.

349. Ammenwerth E, Schnell-Inderst P, Machan C, et al. The effect of electronic prescribing on medication errors and adverse drug events: a systematic review. J Am Med Inform Assoc. 2008;15:585-600.

350. Nuckols T, Smith-Spangler C, Morton S, et al. The effectiveness of computerized order entry at reducing preventable adverse drug events and medication errors in hospital settings: a systematic review and meta-analysis. Syst Rev. 2014;3:56.

351. Kaushal R, Shojania K, Bates D. Effects of computerized physician order entry and clinical decision support systems on medication safety: a systematic review. Arch Intern Med. 2003;263:1409-1416.

352. Genco EK, Forster JE, Flaten H, et al. Clinically Inconsequential Alerts: The Characteristics of Opioid Drug Alerts and Their Utility in Preventing Adverse Drug Events in the Emergency Department. Ann Emerg Med. 2016;67:240-248.e243.

LIST OF TABLES

Treating Physician Discretion according to patient characteristics, local practice preferences, and state law.

Table 4 - Pain Medication Recommended Taper* following a **Non-operative Musculoskeletal Injury** (e.g. closed management of injury, laceration repair, etc.). Dosage and duration can be less if tolerated. *In conjunction with other Best Practice Recommendations and individualized per Treating Physician Discretion according to patient characteristics, local practice preferences, and state law.

Table 5 - Pasero Opioid-induced Sedation Scale (POSS) With Intervention.[282]

Footnotes for Table 1:

N/A not applicable; ISS injury severity scale; ICU intensive care unit; CHD coronary heart disease; CTS carpel tunnel syndrome; MVC motor vehicle crash; ED emergency department; OB/GYN obstetrics and gynecology; TENS transcutaneous electrical nerve stimulation; RCT randomized clinical trial; OA osteoarthritis; TKA total knee arthroplasty; THA total hip arthroplasty; CTSI close soft tissue injury; POD post-operative day; ASA American Society of Anesthesiologists; XR extended release; ACL anterior cruciate ligament; MIS minimally invasive surgery; PLIF post lumbar interbody fusion; ORIF open reductions internal fixation; NSAID non-steroidal anti-inflammatory drug; BSN Bachelor of Science Nursing; ER/LA extended release/long acting; SCOPE Safe and Competent Opioid Prescribing Education; CAS clinical assessment system; COT chronic opioid therapy.

Table 1 - Best Practice Recommendations* for alleviation of acute pain after Musculoskeletal Injury. *In conjunction with Pain Medication Recommendations and individualized per Treating Physician Discretion according to patient characteristics, local practice preferences, and state law.

Category	**Recommendations**
Pain Medication Strategies	• Use multimodal analgesia (MMA). MMA may include non-steroidal anti-inflammatories (NSAIDs), acetaminophen, gabapentinoids, and immediate-release opioids. • Prescribe the lowest effective immediate-release opioid dose for the shortest period possible. • Do not use extended-release opioids. • Consider local or regional block anesthesia as part of the post-operative multimodal regimen.
Cognitive Strategies	• Discuss alleviation of pain, expected recovery course, and patient experience at all encounters. • Connect patients with pain that is greater or more persistent than expected and patients with substantial symptoms of depression, anxiety, or post-traumatic stress or less effective coping strategies (greater catastrophic thinking, lower self-efficacy) to psychosocial interventions and resources. • Consider using strategies for optimal mindset such as aromatherapy, music therapy, or approaches based on cognitive behavioral therapy.
Physical Strategies	• Use immobilization, ice, and elevation appropriately. • Consider the use of transcutaneous electrical stimulation (TENS) units. • Consider the use of cryotherapy units.
Strategies for Patients on Long Term Opioids at Presentation	• Utilize balanced physical, cognitive, and pharmaceutical strategy for alleviation of pain • Ensure that there is only one prescriber by coordinating with acute pain service (APS) (or addiction medicine or psychiatry depending on resources) when inpatient and the patient's prescriber when outpatient.
Pain Assessment Strategies	• Assess pain and sedation regularly for inpatients with short validated tools.
System Strategies	• Query the state and relevant regional Prescription Drug Monitoring Program (PDMP) before prescribing opioids. • Develop and support the implementation of clinical decision support for opioid prescribing in the electronic medical record. • Support opioid education efforts for prescribers and patients. • Implement pain medication prescribing strategy or policy.

Table 2 -Pain Medication Recommended Taper* following a **Major Musculoskeletal Injury Procedure** (e.g. operative fixation of long bone or complex joint fracture, extensive soft tissue injury or surgery, etc.). Dosage and duration can be less if tolerated. *In conjunction with other Best Practice Recommendations and individualized per Treating Physician Discretion according to patient characteristics, local practice preferences, and state law.

Status	**Opioid**	**Non-opioid**
Inpatient		
	Oxycodone/Acetaminophen 5mg/325mg 1 tab po q 4 hours PRN moderate pain 5mg/325mg 2 tabs po q 6 hours PRN severe pain (hold next acetaminophen scheduled dose) Hydromorphone 1mg IV q 3 hours PRN for severe breakthrough pain	Ketorolac 15mg IV q 6 hours x 5 doses, followed by Ibuprofen 600mg po q 8 hours Gabapentin 100mg 1 tab po TID Scheduled Acetaminophen 500mg po q 12 hours
Post Discharge		
Week 1 (at discharge)	Oxycodone/Acetaminophen 5mg/325mg 1 tab po q 4 hours PRN Dispense - #42 (1 time Rx, No Refills)	Ibuprofen 600mg po q 8 hours x 7 days (Rx Given) Gabapentin 100mg 1 tab po TID x 7days (Rx given) Scheduled Acetaminophen 500mg po q12 hours x 7 days (can increase as combined opioid analgesic decreases)
	Hydrocodone/Acetaminophen 5mg/325mg or Tramadol 50mg (Only If Necessary – 3 Rx Max)	NSAIDs PRN as directed Gabapentin if necessary (up to 1800mg/day)
Week 2 Week 3 Week 4	1 tab po q 4 hours PRN Dispense - #42 1 tab po q6 hours PRN Dispense - #28 1 tab po q8 hours PRN Dispense - #21	Scheduled Acetaminophen 500mg po q12 hours (can increase as combined opioid analgesic decreases) Scheduled Acetaminophen 1000mg po q12 hours (can increase as combined opioid analgesic decreases) Scheduled Acetaminophen 1000mg po q8 hours (can increase as combined opioid analgesic decreases)
Weeks 5+		NSAIDs PRN as directed Acetaminophen PRN as directed Gabapentin if necessary (then wean)

Table 3 - Pain Medication Recommended Taper* following a **Minor Musculoskeletal Injury Procedure** (e.g. operative fixation of small bone or simple joint fracture, minimal soft tissue injury or surgery, etc.). Dosage and duration can be less if tolerated. *In conjunction with other Best Practice Recommendations and individualized per Treating Physician Discretion according to patient characteristics, local practice preferences, and state law.

Status	**Opioid**	**Non-opioid**
Post Discharge		
Week 1	Hydrocodone/Acetaminophen 5mg/325mg or Tramadol 50mg 1 tab po q 6 hours PRN Dispense - #28 (1 time Rx, No Refills)	Ibuprofen 600mg po q 8 hours x 7 days (Rx Given) Gabapentin 100mg 1 tab po TID x 7 days (Rx given) Scheduled Acetaminophen 1000mg po q12 hours (can increase as combined opioid analgesic decreases)
Week 2 Week 3	Hydrocodone/Acetaminophen 5mg/325mg or Tramadol 50mg (Only If Necessary – 2 Rx Max) 1 tab po q 8 hours PRN Dispense - #21 1 tab po q12 hours PRN Dispense #14	NSAIDs PRN as directed Gabapentin if Necessary (up to 1800mg/day) Scheduled Acetaminophen 1000mg po q8 hours (can increase as combined opioid analgesic decreases) Scheduled Acetaminophen 1000mg po q8 hours(can increase as combined opioid analgesic decreases)
Weeks 4+		NSAIDs PRN as directed Acetaminophen PRN as directed

Table 4 - Pain Medication Recommended Taper* following a **Non-operative Musculoskeletal Injury** (e.g. closed management of injury, laceration repair, etc.). Dosage and duration can be less if tolerated. *In conjunction with other Best Practice Recommendations and individualized per Treating Physician Discretion according to patient characteristics, local practice preferences, and state law.

Injury Category	**Opioid**	**Non-Opioid**
Minor Injury (e.g. small bone fracture, sprain, laceration, etc.)	Tramadol 50mg (Only If Necessary - 2 Rx Max) 1 tab po q 6 hours PRN Dispense - #20, then #10	NSAIDs PRN as directed Scheduled Acetaminophen 1000mg po q8 hours, then PRN as directed
Major Injury (e.g. large bone fracture, rupture, etc.)	Hydrocodone/Acetaminophen 5mg/325mg or Tramadol 50mg (Only If Necessary – 2 Rx Max) 1 tab po q 6 hours PRN Dispense - #20, then #10	NSAIDs PRN as directed Scheduled Acetaminophen 1000mg po q12 hours, then PRN as directed

Table 5 - Pasero Opioid-induced Sedation Scale (POSS) With Intervention.[282]

Score	Category	Intervention
S	Sleepy, easy to arouse	Acceptable; no action necessary; may increase opioid dose if needed
1	Awake and alert	Acceptable; no action necessary; may increase opioid dose if needed
2	Slightly drowsy, easily aroused	Acceptable; no action necessary; may increase opioid dose if needed
3	Frequently drowsy, arousable, drifts off to sleep during conversation	Unacceptable; monitor respiratory status and sedation level closely until sedation level is stable at less than 3 and respiratory status is satisfactory; decrease opioid dose 25% to 50% or notify prescriber or anesthesiologist for orders; consider administering a non-sedating, opioid-sparing non-opioid, such as acetaminophen or an NSAID, if not contraindicated
4	Somnolent, minimal or no response to verbal or physical stimulation	Unacceptable; stop opioid; consider administering naloxone; notify prescriber or anesthesiologist; monitor respiratory status and sedation level closely until sedation level is stable at less than 3 and respiratory status is satisfactory