TRIPOM
An EBPOM Partner

Dr. Bridger Bach

Dr. William Lane

Duke Anaesthesiology, Duke University School of Anaestheisa, Durham NC, USA

12 Dec 2018

The Perioperative Management of the Chronic Pain Patient – USA Perspective

Key Points

- Perioperative pain is extremely common across the globe
- Chronic pain is associated with increased co-morbidity and complications
- Pain is best managed through multimodal techniques
- This article presents the US perspective on pain management

MCQ

1. Indications for spinal cord stimulation include:
    a. CRPS
    b. Failed back surgery syndrome
    c. Post-operative pain
    d. Post-amputation pain

2. True statements about the implants are:
    a. Diathermy can cause thermal injury to brain or spine
    b. Electrical interference can cause reprogramming of major consequence
    c. Management of device should be discussed during WHO team brief
    d. ICU or HDU admission recommended post-operatively for neurological observation

Dr. Bridger Bach

Dr. William Lane

Duke Anaesthesiology, Duke University School of Anaestheisa, Durham NC, USA

3. Regarding vagal nerve stimulator (VNS), true statements are:
    a. Recommended by NICE for depression
    b. Electrode are implanted on both vagus nerves
    c. Vagal nerve stimulation may worsen obstructive sleep apnoea
    d. Patient with VNS has increased risk of aspiration

4. The following procedures can be performed safely in patients with deep brain stimulator in situ:
    a. MRI scanning
    b. Angiography
    c. Defibrillation
    d. CT scanning

5. MRI scanning can be performed in patients with:
    a. Cochlear implant
    b. Prosthetic heart valve
    c. Total hip replacement
    d. Retinal implant

Answers: 1. TTFT 2. TTTF 3. TFTT 4. FTTT 5. TTTT

Dr. Bridger Bach

Dr. William Lane

Duke Anaesthesiology, Duke University School of Anaestheisa, Durham NC, USA

12 Dec 2018

Introduction

The prevalence of chronic pain varies depending on the definition used. Recent studies on the epidemiology of chronic pain are lacking but the reported incidence ranges from 13 to 55%. [1-4]

- 13 – 49.4% In low- and middle-income countries [1]
- 10-55% In the United States [2]
- 1.5 Billion people worldwide [3]
- 35 – 51.3% of the UK population with a pooled estimate 43.5% [4]

Definitions for chronic pain in published studies include: continuous or recurrent pain persisting beyond expected normal healing time [5], self-reported “chronic pain”, pain lasting greater than 1 month, greater than 3 months, greater than 6 months, greater than 1 year, and pain present on more than 15 days a month [1]. Guidelines from the American Society of Anesthesiologists define chronic pain as pain of any etiology not directly related to neoplastic involvement, associated with a chronic medical condition or extending in duration beyond the expected temporal boundary of tissue injury and normal healing, and adversely affecting the function or well-being of the individual [6]. A definition approved by the Faculty of Pain Medicine, British Pain Society, and Royal College of General Practitioners’ Chronic Pain Lead is pain or discomfort that troubles a person all of the time or on and off for more than 3 months [7, 8].

Regardless of the definition a significant portion of the population suffers from chronic pain, and this can present difficulties in the perioperative period. It is estimated that around 23% of the adult preoperative population uses opioids for pain control [9]. Chronic opioid use is also associated with worse surgical outcomes:

- More likely to experience chronic post-surgical pain (CPSP) not related to previous pain [10]
- Increased hospital length of stay [11]
- Higher 30 day readmission rate [11]
- Increased health care expenditures [11]

Dr. Bridger Bach

Dr. William Lane

Duke Anaesthesiology, Duke University School of Anaestheisa, Durham NC, USA

- Higher postoperative opioid consumption and pain scores [12, 13]
- Worse function outcomes [13]
- Increased morbidity and mortality [14]

Postoperative pain control may be difficult due to central and peripheral sensitization which may be present in patients with chronic pain. Thus analgesia is particularly important in the perioperative period. The goal of preventative anesthesia is attenuation of afferent nociceptive signaling to decrease potential central sensitization. Chronic opioid users may require more opioid postoperatively due to opioid tolerance, a state where higher opioid doses are required to maintain analgesic efficacy. This is thought to occur by a variety of mechanisms including increased metabolism, decreased cellular receptor density, and attenuated signaling cascades [15]. Tolerance occurs to the euphoric, analgesic, respiratory, sedative, and nauseating effects of opioids but not to decreased gastrointestinal motility. Untreated acute pain or abrupt discontinuation of opioids can lead to hemodynamic disturbances including tachycardia and hypertension. The goals of treating patients chronically taking opioids are to provide adequate analgesia, minimize the deleterious side effects of opioids, and to prevent withdrawal.

It is the responsibility of all members of the perioperative team to identify patients at risk for untreated post-operative pain and on chronic opioid therapy. A thorough history and discussion with the patient is essential which should include:

- Current opioid regimen.
- Duration of opioid use.
- Alternative therapies used and their efficacy.
- Prior experiences after procedures.
- Patient expectations and concerns.

Risk factors for uncontrolled post-operative pain or chronic post-surgical pain include “catastrophizing”, negative affect, preoperative pain, perioperative opioid use, and anxiety. Mal-adaptive cognitive styles are associated with exaggerated and negative schema in response to pain. It is related to adverse pain outcomes and accounts for significant variance in pain scores, narcotic usage, and interference with activity.

Dr. Bridger Bach

Dr. William Lane

Duke Anaesthesiology, Duke University School of Anaestheisa, Durham NC, USA

There are numerous pre-operative physical, psychiatric and medical tools that may be employed. Psychiatric tools include resources such as Cognitive Behavioral Therapy (CBT), relaxation therapy and music therapy. In appropriate patients, music therapy can be an effective way of managing anxiety and pain. Music therapy can be used throughout the perioperative period to improve patient coping, and mitigate pain processing and anxiety. Physical tools include physical therapy and preemptive rehabilitation in patients. Nutrition should be optimized as well if indicated. Patients with poor nutritional scores report higher subjective rates of pain in certain populations in addition to the already known risks of surgery in malnourished patients *** Citation.

Research has demonstrated that patients who undergo an opioid wean prior to a surgical procedure have improved functional outcomes and improved pain control following surgery. The 2017 ASIPP guidelines suggest a weekly OME reduction by 10% as tolerated by patient [16]. However, this may be unrealistic due to patient intolerance or surgical time constraints and should be tailored to the situation and patient.

Adjunct Therapies

It is also important to improve analgesia through the use of opioid sparing therapies and multimodal regimens. The following agents have been studied and although evidence of their efficacy when given as a single dose prior to a procedure may be of limited benefit, many permutations may be possible and likely have benefit when used in combination:

Gabapentin:

Gabapentin is structurally similar to GABA. However, it interacts with pre-synaptic voltage-gated calcium channels to influence the release of excitatory neurotransmitters. Studies have found no significant decrease in the incidence of CPSP with preoperative administration of 300-1200 mg [17]. However, post-operative administration of gabapentin does result in prolonged (> 6 hours) reduction of pain scores and decreased opioid requirements. The American Pain Society strongly recommends that gabapentin be considered as part of a multimodal analgesic regimen for acute post-operative pain. Concerns using gabapentin include sedation and dizziness [18].

Dr. Bridger Bach

Dr. William Lane

Duke Anaesthesiology, Duke University School of Anaestheisa, Durham NC, USA

Pregabalin:

Pregabalin is also structurally related to GABA but exerts an effect by binding to voltage-gated calcium channels to inhibit excitatory neurotransmitter release. Studies have found no significant decrease in the incidence of CPSP with preoperative administration of 150-300 mg [17]. Although not effective for CPSP prevention it is associated with reduced post-operative opioid requirements and an effective addition to a multimodal pain regimen. Concerns using pregabalin are similar to gabapentin [18].

Acetaminophen:

The mechanism of acetaminophen is not fully understood but is thought to cause serotonergic inhibition of descending CNS signaling. When used as part of a multimodal pain regimen acetaminophen is associated with decreased post-operative pain scores and opioid consumption [18]. Acetaminophen should be used in caution in patients with liver disease and the dose should be reduced to 2-3 g/day. It is contraindicated in severe hepatic impairment and active liver disease.

Nonsteroidal Antiinflammatory Drugs (NSAIDs):

NSAIDs function by COX inhibition leading to decreased conversion of arachidonic acid to prostaglandins, prostacyclins and TXA-2 which modulate vascular tone, vascular permeability and platelet aggregation. The two COX isoforms are COX-1 and COX-2. In addition to its other functions the COX-2 isoform is involved in the inflammatory response and an important target of NSAIDs. Due to the homology between the two enzymes different NSAIDs effect the isoforms to various degrees and lead to the toxicities of various NSAID agents. Ibuprofen reversibly inhibits both COX isoforms to reduce prostaglandin production leading to decreased inflammation and analgesia. A commonly studied dose of ibuprofen is 400 mg prior to surgery. Studies have not demonstrated a significant decrease in CPSP. Post-operative administration of ibuprofen is associated with lower pain scores. NSAIDs should be used with caution in the perioperative period. Use of non-selective agents should be avoided in patients with a history of GI ulcers or hemorrhage, concurrent glucocorticoids, on an antiplatelet / anticoagulation therapy due to concerns about GI bleeding. NSAID use may also be associated with anastomotic leak after colorectal surgery [19]. NSAIDs may also impair renal function. Prostaglandins promote renal artery dilation and maintain renal perfusion, which is particularly important in states of renal hypoperfusion (adrenergic stimulation, hypovolemia, hypotension, CHF, cirrhosis etc). They should also be avoided in patients with pre-existing renal disease or impairment, and in

Dr. Bridger Bach

Dr. William Lane

Duke Anaesthesiology, Duke University School of Anaestheisa, Durham NC, USA

surgeries where nephrotoxic medications may be administered. Selective COX-2 NSAIDs also lead to impairment of renal function [20]. NSAIDs increase the risk of MI and stroke, and use is contraindicated in patients undergoing coronary artery bypass graft surgery. There exists concern about the use of NSAIDs with orthopedic surgeries after animal studies suggested an association between NSAID use and bone non-union. However, analysis of higher-quality studies have not demonstrated a statistically significant increase in non-union with spinal fusion procedures [21]. Selective COX-2 inhibitors such as celecoxib are associated with lower rates of GI ulcer formation, and at usual doses do not significantly impair platelet aggregation.

Lidocaine:

The mechanism by which intravenous lidocaine is hypothesized to exert its effect is via interference with molecular targets involved in the inflammatory cascade (such as mitigating the release of cytokines and inflammatory mediators by PMN's) as well as blocking excitatory neuronal responses [22]. Intraoperative or postoperative lidocaine can be an addition to a multimodal pain regimen. A 2018 meta-analysis of 66 trials comparing lidocaine to placebo found uncertain results whether the infusion reduces pain (at 1-4, 24, and 48 hours after surgery), improves recovery of bowel function, reduces post-operative nausea, or opioid requirements. Commonly studied doses include an initial bolus of 1.5 – 2 mg/kg followed by an intraoperative infusion from 1.5 – 3 mg/kg/hour [23]. The APS recommends IV lidocaine be considered as part of a multimodal regimen in patient's without contraindications based on meta-analysis published in 2008 and 2011 [18].

Ketamine:

Ketamine is an arylcyclohexylamine, chemically related to phencyclidine, which acts through non-competitive NMDA antagonism to decrease excitatory neuronal signaling. One of the proposed mechanisms behind the development of opioid tolerance and hyperalgesia is activiation of the NMDA receptor. Ketamine is one of the few studied agents that is associated with a small but statistically significant decrease in incidence of CPSP when used for longer than 24 hours following surgery [17]. The APS recommends ketamine as part of a multimodal pain regimen. Some studies demonstrate lower post-operative pain scores, and it is associated with reduced post-operative pain medication requirements compared to placebo. Studies vary based on pre-incisional bolus (0.15 – 2 mg/kg), intraoperative infusion (0.12 mg/kg/h – 2 mg/kg/h), bolus at closure (0.15 – 2 mg/kg), and postoperative infusion

Dr. Bridger Bach

Dr. William Lane

Duke Anaesthesiology, Duke University School of Anaestheisa, Durham NC, USA

doses. The APS recommends a preoperative bolus of 0.5 mg/kg followed by a 10 µg/kg/min intraoperative infusion, and potential a post-operative infusion[18].

Magnesium:

Magnesium is hypothesized to provide analgesia through NMDA antagonism. A 2013 meta-analysis of 20 RCT's found that pain was decreased at rest (but not movement) 0-4 hours after surgery with an intraoperative magnesium infusion. Pain was also decreased 24 hours after surgery in patients who received both intraoperative and post-operative infusions (but not in patients who only received an intraoperative infusion). Opioid requirements were decreased in both groups (intraoperative vs intraoperative and postoperative infusions) with a mean difference of 10.5 mg oral morphine equivalents (11 in the group both intra and post-op compared to 7.8 intra-op alone) [24]. The APS does not provide a recommendation about the use of intravenous magnesium but strongly recommends against its neuraxial administration [18].

Dexmedetomidine:

Dexmedetomidine is a selective alpha 2 adrenergic receptor agonist leading to dose-dependent sedation and analgesia without respiratory impairment. Data on the analgesic efficacy of perioperative dexmedetomidine varies. A 2016 Cochrane meta-analysis determined that it was difficult to draw conclusions of perioperative dexmedetomidine infusions based on the limited data available. However, there appeared to be an decrease in opioid rescue requirement without an associated decrease in reported pain scores [25]. More recently, a 2018 meta-analysis found that compared to placebo dexmedetomidine decreased pain scores and opioid consumption within 24 hours after surgery [26].

Clonidine:

Clonidine is a selective alpha 2 adrenergic receptor agonist resulting in reduced CNS sympathetic signaling. Analgesia from clonidine may be from inhibition of pain signal transmission at presynaptic and postjunctional adrenorecptors. A 2012 meta-analysis included 19 studies that evaluated the analgesic efficacy of both oral and intravenous clonidine. Clonidine significantly decreased the oral morphine equivalent consumption at 12 (20.3 mg in treatment group vs 30.1 mg in controls) and 24 hours (12.6 mg in treatment group vs 16.7 mg in controls), but not < 12 hours following the procedure. 12 and 24 hour postoperative pain scores were also significantly lower in the treatment arm, but pain

Dr. Bridger Bach

Dr. William Lane

Duke Anaesthesiology, Duke University School of Anaestheisa, Durham NC, USA

scores were not significantly different < 12 hours following the procedure. Clonidine was more likely to cause hypotension with a number needed to harm of 9 [27]. Clonidine may also be used as an adjuvant to prolong peripheral neural blockade, or co-administered with neuraxial local anesthetics. A 2013 meta-analysis found that intrathecal clonidine decreased post-operative opioid requirements (mean reduction of 4.45 mg) but increased the incidence of hypotension [28].

Medication	**Preoperative Administration**	**Postoperative Administraiton**
Gabapentin	300-1200 mg in preoperative period. No significant change in CPSP incidence.	250-500 mg. NNT of 11 for 50% analgesia with 250 mg. Decreased opioid requirement with post-op administration.
Pregabalin	75-300 mg. Reduces pain scores, and opioid consumption reduced with all doses at 24 hours. (Mishriky, 2015, British Journal of Anesthesia).	Pain scores at rest reduced with multiple dosing but modest effect. No significant decrease in post-operative opioid consumption with post-operative dosing.
Acetaminophen	Limited/low quality data supporting premedication. May reduce post-operative opioid requirements.	Oral: 500-1000 mg. NNT for 50% pain relief 3.5 with 500 mg, 3.6 with 1000 mg. Single dose provides effective analgesia for ~ ½ of patients for about 4 hours. IV: 36% of patients received 50% analgesia over 4 hours. Decreased opioid requirement by 26% over 4 hours. High-quality evidence.
NSAIDs	Ibuprofen 400 mg in preoperative period, no significant decrease in CPSP. Celecoxib: 200-400 mg. Significant post-operative opioid requirement. (Nir, 2016, European Journal of Pain).	Ibuprofen: 200-400 mg. NNT for 50% relief 2.7 with 200 mg and 2.5 for 400 mg. High-quality evidence. Diclofenac: 50 mg. NNT for 50% relief 2.1. Celecoxib: 200-400 mg. NNT for 50% relief 4.2 with 200 mg and 4.2 for 400 mg. Aspirin: 300-1200 mg. NNT for 50% relief 4.2 with 650 mg, 3.8 with 1000 mg, and 2.7 with 1200 mg. Naproxen: 200-500 mg. No dose response with < 500 mg. NNT for 50% relief 2.7 with 500 mg..
Lidocaine	Initial bolus of 1.5 – 2 mg/kg, followed by infusion of 1-5 mg/kg/hr. Unlikely to provide meaningful analgesia at < 24 hours. Low quality evidence available (inconsistency, imprecision, study quality).	
Ketamine	Bolus of 0.1-0.5 mg/kg and infusion of 0.1-0.6 mg/kg/hr during and 24 hours following surgery. Small but significant reductions in pain. (Schwenk 2018, Regional Anesthesia and Pain Medicine)	
Magnesium	Bolus 30-50 mg/kg with infusion 10 mg/kg/hr over several hours. Intraoperative administration +/- intraoperative and postoperative infusions associated with decreased pain and opioid requirements (~10.5 mg OME). (De Oliveira 2013)	

Dr. Bridger Bach

Dr. William Lane

Duke Anaesthesiology, Duke University School of Anaestheisa, Durham NC, USA

Dexmedetomidine	May decrease pain scores and opioid consumption following surgery. 0.5-1 mcg/kg followed by 0.2-0.8 mcg/kg/h infusion.
Clonidine	Studied regimens include PO 300 mcg preoperatively 60 minutes prior to procedure. 5 mcg/kg + 0.3 mcg/kg/h for 11 hours. 3 mcg/kg 15 minutes prior to procedure. Associated with decreased opioid consumption and lower pain scores, but increased incidence of hypotension. (Blaudszun 2012, Anesthesiology).

Regional Anesthesia

For appropriate procedures the use of regional anesthesia can be associated with improved perioperative outcomes. In patients on chronic opioid therapy, there is a reduction in opioid use and superior postoperative analgesia [29].

Single injections peripheral nerve blocks provide effective pain control, however are limited by relatively short hour duration of analgesia. They typically show improvement in verbal analog pain scores and opioid consumption 12-24 hours after procedure, with variation depending on the location of block and choice of local anesthetic [30]. Continuous peripheral nerve blockade offers prolonged analgesia, lower opioid consumption, and better patient satisfaction [31]. Nevertheless, a single injection can still be of benefit in scenarios when a catheter might not be feasible.

Special Considerations

Patients may be prescribed certain medications that could alter perioperative management including:

Buprenorphine:

Buprenorphine is a partial mu agonist that was initially used to treat opioid addiction but is now also employed in the treatment of chronic pain disorders [32]. Buprenorphine binds with high affinity for the mu opioid receptor but with low intrinsic activity leading to a plateau effect with higher doses. It is a kappa and delta antagonist. Because of the partial agonist and kappa / delta antagonism there is minimal respiratory depression from buprenorphine. There are oral, sublingual, transdermal, subcutaneous, IM and IV formulations. The half-life of the sublingual tablet is 37 hours, transdermal patch around 26

Dr. Bridger Bach

Dr. William Lane

Duke Anaesthesiology, Duke University School of Anaestheisa, Durham NC, USA

hours, and of the buccal film around 27 hours. Due to the high-affinity of buprenorphine to the opioid receptor these patients may require more full opioid agonist. If buprenorphine is not continued postoperatively these doses should be titrated to prevent over-sedation and respiratory depression. Preoperative treatment strategies will differ depending on the elective or emergent nature of surgery, and should be discussed with the buprenorphine prescriber. Providers may choose to discontinue buprenorphine and transitioning to a full agonist (methadone or short acting opioid), continue buprenorphine and supplement with multimodal therapy and additional opioids as required, or increase the dose of buprenorphine. Anderson et al. detail treatment algorithms for elective and emergency surgery in Anesthesiology that may help guide preoperative management [33].

Methadone:

While many patients and health care providers continue to associate methadone with its role in drug rehabilitation, it has been used as an effective agent for pain control. It is structurally unrelated to other opium-derived alkaloids, with a d-isomer that antagonizes the NMDA receptors, blocks human ether-a-gogo related gene, inhibits serotonin and norepinephrine reuptake, and is an opioid agonist. Methadone is known for unpredictable bioavailability, rapid onset and longer duration compared to SROs. Comparing its equianalgesic dosing is challenging due to its variability, lack of uniform guidelines, as well as NMDA activity. Management of patients on chronic methadone can be challenging. Like other opioids, methadone should be weaned prior to surgery. The magnitude and time course of wean is unclear at this point. Some have argued that a patient's dose of methadone should not be changed in the perioperative setting to prevent fluctuations in drug level [34]. Patients on methadone are risked for prolonged QT interval, and careful review of recent EKG is needed. Some providers have adopted the practice of using intraoperative methadone to provide quick onset analgesia that will provide relief into the post-operative phrase. It has been argued that Methadone can improve analgesia in patients after complex spine procedures [35]. A single dose of 20 mg at induction can potentially improve pain up until POD 1-2.

Postoperative Course

Patient on chronic opiate therapy may have higher post-operative analgesic requirements. Compared to opioid naïve patients, postoperative pain scores may be higher and decrease at a slower rate [36]. There is no universal approach for a patient's postoperative opiate needs, and a regimen should be customized for the patient based on

Dr. Bridger Bach

Dr. William Lane

Duke Anaesthesiology, Duke University School of Anaestheisa, Durham NC, USA

12 Dec 2018

their needs during admission. A multimodal pain regimen including the adjuncts discussed above should be instituted. It is not uncommon for opioid requirements to increase by 30 to 50% in the post-operative setting [37]; however, some anecdotal studies have found that patients who undergo an opioid wean prior to surgery may actually have lower long-term postoperative opioid requirements if they undergo a preoperative opioid wean. If the surgery was performed to address the source of the patients pain they may tolerate a rapid wean. When assessing pain scores, it is vital to compare a patient's postoperative scores to pre-operative pain scores. If pain scores escalate or fail to decline in the postoperative setting, other reasons for pain including surgical complications should be considered.

In reliable, non-delirious patients patient controlled analgesia (PCA) has been associated with increased patient satisfaction and perception over pain control [38]. Advantages of PCA are rapid pain relief due to not having to wait for nurse delivered analgesia, theoretical stable plasma concentrations and avoidance of peak concentrations that may lead to respiratory depression. PCA also allows for trending of the patients opioid requirement, and conversion to an equivalent oral regimen when oral intake is tolerated.

Regardless of the mode of delivery, monitoring for opioid related side effects is vital in this setting. While tolerance to analgesia and the side effects of opioids can be evident, rapid escalation of opioid doses can still lead to respiratory depression.

Prevention of withdrawal must also be considered. Symptoms include anxiety, muscle aches, lacrimation, diarrhea, and abdominal cramping. The primary aspects management include identification of risk, drug replacement, and symptom management. Only a small dose of opioid, less than 50% of preoperative dose, is needed to prevent withdrawal. Clonidine has been commonly used to manage opioid withdrawal, although sedation and hypotension may be more frequent [39].

Following discharge, a taper should be created in order to wean a patient back to a medication regimen that will control the patient's pain and also allow them to be functional. Considerations including expected timetable for resolution of post surgical pain, choice of new analgesic agents, potential risks of increased opioid dosing, and effective communication with the patient's outpatient medical providers. The team should discuss

Dr. Bridger Bach

Dr. William Lane

Duke Anaesthesiology, Duke University School of Anaestheisa, Durham NC, USA

this taper with the patient early in the discharge planning process to help create appropriate expectations.

Summary

Opioid tolerant patient suffering from chronic pain have worse outcomes including chronic post-surgical pain, increased morbidity, and increased mortality. Thus, it is important to identify patients in the preoperative setting who have chronic pain, or are likely to have difficult-to-treat post-operative pain. Once identified these patients should be managed by formal chronic pain teams as part of a perioperative pathway who assist in caring for these patients in both the preoperative and postoperative setting. Although data supporting the use of any single adjunct therapy varies, multimodal opioid-sparing regimens should be employed to manage these patients.

References:

1. [1] T. Jackson, S. Thomas, V. Stabile, M. Shotwell, X. Han, and K. McQueen, "A Systematic Review and Meta-Analysis of the Global Burden of Chronic Pain Without Clear Etiology in Low- and Middle-Income Countries: Trends in Heterogeneous Data and a Proposal for New Assessment Methods," (in eng), *Anesth Analg,* vol. 123, no. 3, pp. 739-48, Sep 2016.
2. [2] R. L. Nahin, "Estimates of pain prevalence and severity in adults: United States, 2012," (in eng), *J Pain,* vol. 16, no. 8, pp. 769-80, Aug 2015.
3. [3] F. Yaqub, "Pain in the USA: states of suffering," (in eng), *Lancet,* vol. 386, no. 9996, p. 839, Aug 29 2015.
4. [4] A. Fayaz, P. Croft, R. M. Langford, L. J. Donaldson, and G. T. Jones, "Prevalence of chronic pain in the UK: a systematic review and meta-analysis of population studies," (in eng), *BMJ Open,* vol. 6, no. 6, p. e010364, Jun 20 2016.
5. [5] "Classification of chronic pain. Descriptions of chronic pain syndromes and definitions of pain terms. Prepared by the International Association for the Study of Pain, Subcommittee on Taxonomy," (in eng), *Pain Suppl,* vol. 3, pp. S1-226, 1986.
6. [6] "Practice guidelines for chronic pain management: an updated report by the American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine," (in eng), *Anesthesiology,* vol. 112, no. 4, pp. 810-33, Apr 2010.

Dr. Bridger Bach

Dr. William Lane

Duke Anaesthesiology, Duke University School of Anaestheisa, Durham NC, USA

7. [7] R. C. o. Anaesthetists. (June 29). *UK Pain Messages*. Available: http://www.rcoa.ac.uk/document-store/uk-pain-messages
8. [8] S. Bridges, "Chronic Pain," vol. Chapter 9, ed: National Health Service, 2011.
9. [9] P. E. Hilliard *et al.*, "Prevalence of Preoperative Opioid Use and Characteristics Associated With Opioid Use Among Patients Presenting for Surgery," (in eng), *JAMA Surg,* Jul 11 2018.
10. [10] E. G. VanDenKerkhof *et al.*, "Impact of perioperative pain intensity, pain qualities, and opioid use on chronic pain after surgery: a prospective cohort study," (in eng), *Reg Anesth Pain Med,* vol. 37, no. 1, pp. 19-27, Jan-Feb 2012.
11. [11] J. F. Waljee, D. C. Cron, R. M. Steiger, L. Zhong, M. J. Englesbe, and C. M. Brummett, "Effect of Preoperative Opioid Exposure on Healthcare Utilization and Expenditures Following Elective Abdominal Surgery," (in eng), *Ann Surg,* vol. 265, no. 4, pp. 715-721, Apr 2017.
12. [12] S. R. Smith, J. Bido, J. E. Collins, H. Yang, J. N. Katz, and E. Losina, "Impact of Preoperative Opioid Use on Total Knee Arthroplasty Outcomes," (in eng), *J Bone Joint Surg Am,* vol. 99, no. 10, pp. 803-808, May 17 2017.
13. [13] R. Pivec, K. Issa, Q. Naziri, B. H. Kapadia, P. M. Bonutti, and M. A. Mont, "Opioid use prior to total hip arthroplasty leads to worse clinical outcomes," (in eng), *Int Orthop,* vol. 38, no. 6, pp. 1159-65, Jun 2014.
14. [14] M. E. Menendez, D. Ring, and B. T. Bateman, "Preoperative Opioid Misuse is Associated With Increased Morbidity and Mortality After Elective Orthopaedic Surgery," (in eng), *Clin Orthop Relat Res,* vol. 473, no. 7, pp. 2402-12, Jul 2015.
15. [15] S. Mitra and R. S. Sinatra, "Perioperative management of acute pain in the opioid-dependent patient," (in eng), *Anesthesiology,* vol. 101, no. 1, pp. 212-27, Jul 2004.
16. [16] L. C. Nguyen, D. C. Sing, and K. J. Bozic, "Preoperative Reduction of Opioid Use Before Total Joint Arthroplasty," (in eng), *J Arthroplasty,* vol. 31, no. 9 Suppl, pp. 282-7, Sep 2016.
17. [17] L. E. Chaparro, S. A. Smith, R. A. Moore, P. J. Wiffen, and I. Gilron, "Pharmacotherapy for the prevention of chronic pain after surgery in adults," (in eng), *Cochrane Database Syst Rev,* no. 7, p. Cd008307, Jul 24 2013.
18. [18] R. Chou *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

Dr. Bridger Bach

Dr. William Lane

Duke Anaesthesiology, Duke University School of Anaestheisa, Durham NC, USA

Anesthesia, Executive Committee, and Administrative Council," (in eng), *J Pain,* vol. 17, no. 2, pp. 131-57, Feb 2016.

19. [19] J. Rutegard and M. Rutegard, "Non-steroidal anti-inflammatory drugs in colorectal surgery: A risk factor for anastomotic complications?," (in eng), *World J Gastrointest Surg,* vol. 4, no. 12, pp. 278-80, Dec 27 2012.
20. [20] V. Schneider, L. E. Levesque, B. Zhang, T. Hutchinson, and J. M. Brophy, "Association of selective and conventional nonsteroidal antiinflammatory drugs with acute renal failure: A population-based, nested case-control analysis," (in eng), *Am J Epidemiol,* vol. 164, no. 9, pp. 881-9, Nov 1 2006.
21. [21] E. R. Dodwell *et al.*, "NSAID exposure and risk of nonunion: a meta-analysis of case-control and cohort studies," (in eng), *Calcif Tissue Int,* vol. 87, no. 3, pp. 193-202, Sep 2010.
22. [22] L. K. Dunn and M. E. Durieux, "Perioperative Use of Intravenous Lidocaine," *Anesthesiology,* vol. 126, pp. 729-737, 2017.
23. [23] S. Weibel *et al.*, "Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery in adults," (in eng), *Cochrane Database Syst Rev,* vol. 6, p. Cd009642, Jun 4 2018.
24. [24] G. S. De Oliveira, Jr., L. J. Castro-Alves, J. H. Khan, and R. J. McCarthy, "Perioperative systemic magnesium to minimize postoperative pain: a meta-analysis of randomized controlled trials," (in eng), *Anesthesiology,* vol. 119, no. 1, pp. 178-90, Jul 2013.
25. [25] L. Jessen Lundorf, H. Korvenius Nedergaard, and A. M. Møller, "Perioperative dexmedetomidine for acute pain after abdominal surgery in adults," *Cochrane Database of Systematic Reviews,* 2016.
26. [26] X. Wang, N. Liu, J. Chen, Z. Xu, F. Wang, and C. Ding, "Effect of Intravenous Dexmedetomidine During General Anesthesia on Acute Postoperative Pain in Adults: A Systematic Review and Meta-analysis of Randomized Controlled Trials," (in eng), *Clin J Pain,* May 16 2018.
27. [27] G. Blaudszun, C. Lysakowski, N. Elia, and M. R. Tramer, "Effect of perioperative systemic alpha2 agonists on postoperative morphine consumption and pain intensity: systematic review and meta-analysis of randomized controlled trials," (in eng), *Anesthesiology,* vol. 116, no. 6, pp. 1312-22, Jun 2012.

Dr. Bridger Bach

Dr. William Lane

Duke Anaesthesiology, Duke University School of Anaestheisa, Durham NC, USA

28. [28] E. Engelman and C. Marsala, "Efficacy of adding clonidine to intrathecal morphine in acute postoperative pain: meta-analysis," (in eng), *Br J Anaesth,* vol. 110, no. 1, pp. 21-7, Jan 2013.

29. [29] J. M. Richman *et al.*, "Does continuous peripheral nerve block provide superior pain control to opioids? A meta-analysis," (in eng), *Anesth Analg,* vol. 102, no. 1, pp. 248-57, Jan 2006.

30. [30] A. Al-Kaisy *et al.*, "Analgesic effect of interscalene block using low-dose bupivacaine for outpatient arthroscopic shoulder surgery," (in eng), *Reg Anesth Pain Med,* vol. 23, no. 5, pp. 469-73, Sep-Oct 1998.

31. [31] M. J. Fredrickson, S. Krishnan, and C. Y. Chen, "Postoperative analgesia for shoulder surgery: a critical appraisal and review of current techniques," (in eng), *Anaesthesia,* vol. 65, no. 6, pp. 608-24, Jun 2010.

32. [32] D. P. Alford, P. Compton, and J. H. Samet, "Acute pain management for patients receiving maintenance methadone or buprenorphine therapy," (in eng), *Ann Intern Med,* vol. 144, no. 2, pp. 127-34, Jan 17 2006.

33. [33] T. A. Anderson, A. N. A. Quaye, E. N. Ward, T. E. Wilens, P. E. Hilliard, and C. M. Brummett, "To Stop or Not, That Is the Question: Acute Pain Management for the Patient on Chronic Buprenorphine," (in eng), *Anesthesiology,* vol. 126, no. 6, pp. 1180-1186, Jun 2017.

34. [34] P. W. Peng, P. S. Tumber, and D. Gourlay, "Review article: perioperative pain management of patients on methadone therapy," (in eng), *Can J Anaesth,* vol. 52, no. 5, pp. 513-23, May 2005.

35. [35] E. D. Kharasch, "Intraoperative methadone: rediscovery, reappraisal, and reinvigoration?," in *Anesth Analg*, vol. 112no. 1) United States, 2011, pp. 13-6.

36. [36] S. E. Rapp, L. B. Ready, and M. L. Nessly, "Acute pain management in patients with prior opioid consumption: a case-controlled retrospective review," (in eng), *Pain,* vol. 61, no. 2, pp. 195-201, May 1995.

37. [37] P. Richebe and P. Beaulieu, "Perioperative pain management in the patient treated with opioids: continuing professional development," (in eng

38. fre), *Can J Anaesth,* vol. 56, no. 12, pp. 969-81, Dec 2009.

39. [38] E. D. McNicol, M. C. Ferguson, and J. Hudcova, "Patient controlled opioid analgesia versus non-patient controlled opioid analgesia for postoperative pain," (in eng), *Cochrane Database Syst Rev,* no. 6, p. Cd003348, Jun 2 2015.

Dr. Bridger Bach

Dr. William Lane

Duke Anaesthesiology, Duke University School of Anaestheisa, Durham NC, USA

40. [39] B. L. Honey, R. J. Benefield, J. L. Miller, and P. N. Johnson, "Alpha2-receptor agonists for treatment and prevention of iatrogenic opioid abstinence syndrome in critically ill patients," (in eng), *Ann Pharmacother,* vol. 43, no. 9, pp. 1506-11, Sep 2009.