Southern California CSU DNP Consortium

California State University, Fullerton
California State University, Long Beach
California State University, Los Angeles

EVIDENCE-BASED ANALGESIA FOR OPIOID DEPENDENT PATIENTS UNDERGOING MAJOR SURGERY

A DOCTORAL PROJECT

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By

Sandra Kay Bordi

Doctoral Project Committee Approval:

Dana Rutledge, PhD, RN, Project Chair
John Nagelhout, PhD, RN, CRNA, Committee Member

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ABSTRACT

There is a high prevalence of chronic pain in America that has resulted in the increased use of opioids for treatment. Healthcare providers are challenged with alleviating acute surgical pain in chronic opioid dependent patients undergoing major surgery. These challenges are due to physical dependence, opioid tolerance, and/or opioid induced hyperalgesia. Results of an integrative literature review indicate that current published practice recommendations (guidelines) are based primarily on secondary sources, case reports, and expert opinion. The medicinal therapies that were reviewed included multimodal analgesia (with and without ketamine), intravenous lidocaine, fentanyl challenge, and methadone. Of these, the evidence supports the use of ketamine when used as adjunctive therapy in a multimodal regimen, and the use of intravenous lidocaine for abdominal surgeries. Further research is recommended for medicinal modalities in alleviating acute surgical pain in chronic opioid dependent patients undergoing major surgery.
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1. Conceptual framework for pathophysiology changes with opioid dependence
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BACKGROUND

It is estimated that approximately 100 million Americans are affected by chronic pain, making it a public health concern (Institute of Medicine of the National Academies, 2011, p. 19). Because of the increasing recognition of chronic pain as a treatable condition, there has also been a significant increase in opioid therapy (Cahana, Danise, Theodore, Wilson, & Turk, 2013). Boudreau et al. (2009) reported that in two major group health plans located in the western United States, the long-term use of opioids doubled from 1997 to 2005.

It is likely that persons in chronic pain who are medicated with opioids for their chronic pain syndrome will require some type of surgical procedure. Anesthesia providers may find this state of chronic opioid dependence among chronic pain patients problematic in terms of treatment of acute surgical pain. Anesthesia providers are generally knowledgeable in treating acute surgical pain in opioid naïve patients. However, when confronted with a patient with opioid dependence, anesthesia providers can encounter challenges. Patients with chronic pain may be on complex medical regimens as part of their treatment plan, resulting in significant potential anesthetic-medications interactions. Other challenges are due to the pre-operative anxiety, depression, and/or a lack of trust in the health care system that may be exhibited by these patients. In addition, patients with preoperative chronic pain are at increased risk for higher levels of acute postsurgical pain (Sommer et al., 2010; VanDenKerkhof et al., 2012). Therefore, it is important that acute surgical pain be treated optimally in chronic pain patients who are opioid dependent. Unfortunately, there has been a lack of evidence-based literature that guides anesthesia providers regarding optimal treatment
modalities for the treatment of acute surgical pain in chronic opioid dependent patients undergoing surgical procedures. Presented with patients with opioid dependencies, anesthesia providers must address acute changes in vital signs with less emphasis on long-term case management. These clinical challenges may result in inadequate pain relief accompanied by patient dissatisfaction, longer postoperative recovery, and the potential for chronic postsurgical pain (Sommer et al., 2010; VanDenKerkhof et al., 2012).

An initial review of the literature revealed a lack of studies focused on the treatment of acute surgical pain in chronic opioid dependent patients. Treatment guidelines that were published stem from expert opinion and case reports rather than empirical evidence (Davis et al., 2003; Mitra & Sinatra, 2004; Rozen & Grass, 2005). Therefore, the primary objective of this project was to conduct a thorough literature review on the efficacy of different modalities of acute pain relief in chronic opioid dependent patients undergoing major surgical procedures. In addition, the secondary objective was to suggest treatment recommendations for acute pain management for chronic opioid dependent patients based upon the literature review and expert opinion.

**Supporting Framework**

The framework used in this project focused on the pathophysiological changes that occur with opioid dependency and how they affect the management of chronic opioid dependent patients undergoing surgery with general anesthesia. A schematic model that conceptualizes the major concepts is shown in Figure 1.
Chronic Pain Patients

Opoid Dependence

Pathophysiologic Changes
1. Tolerance
2. Dependence
3. Opioid-induced hyperalgesia

Surgery that requires General Anesthesia

Adequate Intraoperative Pain Relief

Inadequate Intraoperative Pain Relief

Adequate Postoperative Pain Relief

Inadequate Postoperative Pain Relief

Type of opioid
-Dosage
-Duration

-Psychiatric history
-Current comorbidities
-Other medications

Knowledge gap
-Stigma

Figure 1. Schematic model of the framework for the pathophysiology changes with chronic opioid dependence and their effect on acute surgical pain management.
Currently, a nationwide concern exists regarding the rise in chronic pain patients who are being prescribed long-term opioids (Boudreau et al., 2009; Campnell et al., 2010). Chronic opioid intake produces underlying changes in body systems that present challenges to anesthesia care providers in treating acute surgical pain during general anesthesia.

The biologic effects of opioids are similar to the endogenous endorphins, enkephalins, and dynorphins. They bind to opioid receptors (mu, delta, and kappa), located centrally and peripherally, thereby producing their analgesic effects (Wilson, 2010). Common effects of opioids include constipation, respiratory depression, sedation, euphoria, nausea and vomiting, urinary retention, and pruritus (Wilson, 2010). Long-term use of opioids results in changes at the cellular level that affect multiple organ systems (Bajwa, 2012; Painter & Crofford, 2013).

Physical dependence is a case in point. Dependence is a pharmacologic phenomenon that is demonstrated when an opioid is abruptly stopped or discontinued with subsequent symptoms of withdrawal (Swift & Lewis, 2008). Withdrawal symptoms consist of sympathetic nervous system responses such as restlessness, anxiety, sweating, dilated pupils, nausea, vomiting, diarrhea, fever, and tachycardia (Fishman, Condon, & Holtsman, 2004). Therefore, it is critical that anesthesia providers identify patients who are opioid dependent prior to a surgical experience. Unfortunately, it is difficult to distinguish every patient who is taking opioids chronically.

Another example of a physiologic change that occurs with long-term opioid intake is opioid-induced hyperalgesia (OIH). It is reliably demonstrated in animal studies (Fishbain, Cole, Lewis, Gao, & Rosomoff, 2009; Tompkins & Campbell, 2011).
However, there is limited research documenting the development of OIH in humans. Even so, case reports (S. Lee et al., 2013; Vorobeychik, Chen, Bush, & Mao, 2008) corroborate that OIH may be clinically significant in chronic opioid dependent patients. The mechanism of action underlying OIH is not clearly understood, but there are several theories. It is thought that sensitization of peripheral nerve endings, enhanced production and release of nociceptive neurotransmitters, sensitization of second-order neurons, and central activation of NMDA and glutamate may play a role in OIH (Angst & Clark, 2006; M. Lee, Silverman, Hansen, Patel, & Manchikanti, 2011; Tompkins & Campbell, 2011). Patients with OIH become more sensitive to pain as a result of chronic opioid therapy (Angst & Clark, 2006). It is difficult to distinguish between OIH and opioid tolerance, since both present clinically as a need for dose escalation. However, OIH is not relieved with increasing doses of opioids. Treatment of OIH includes dose reduction and implementing non-opioid analgesics (Bordi, 2014). Therefore, treating acute surgical pain in the presence of OIH can be difficult with limited medication options.

Lastly, opioid tolerance occurs with chronic opioid use. Opioid tolerance is defined as the need for additional opioid dosages (concentrations) in order to achieve an analgesic effect (Swift & Lewis, 2008). Tolerance may be the result of several mechanisms, such as up-regulation of adenylyl cyclase with continued opioid administration or down-regulation of opioid receptors (M. Clark & Traynor, 2005). Other mechanisms involved with tolerance continue to be debatable and include changes in drug-receptor interactions, intracellular alterations, opioid receptor desensitization as well as long term adaptations in gene expression (Bordi, 2014; M. Clark & Traynor, 2005; Hull et al., 2010; Zhu, Badisa, Palm, & Goodman, 2012). The development of tolerance
to an opioid is an adaptive physiologic response. When tolerance to an opioid occurs, opioid rotation is suggested. This involves switching from one opioid to another in an effort to improve analgesia and decrease side effects (Bordi, 2014). Similar to OIH, alleviating acute surgical pain can be challenging in patients with opioid tolerance.

Other factors that impact the physiologic changes with chronic opioid intake are the type of opioid, method of administration, and its duration of intake. Likewise, concomitant ingestion of other medications can have an effect on the body, producing further adverse effects. Furthermore, since many opioids are metabolized by the liver and excreted via the kidneys, co-existing hepatic or renal disease can inadvertently result in changes in opioid clearance and life threatening side effects.

**Project Goals**

The primary issue that triggered this doctoral project was the potential inadequacy of intraoperative and postoperative acute surgical pain management in chronic opioid patients. The one goal/outcome to address this problem was to identify the different pharmacologic modalities and their efficacy in chronic opioid dependent patients. In order to accomplish this, an in depth literature review was initiated. Case reports, research studies, textbooks, and professional expert opinion were explored. In addition, a secondary outcome for this project was to develop a treatment guideline for acute surgical pain management in chronic opioid dependent patients based on the evidence review.

The secondary problem identified was the knowledge gap of anesthesia providers regarding the physiologic changes that occur with opioid dependency and how these may affect the management of chronic opioid dependent patients undergoing surgery with general anesthesia. To address this problem, physiologic changes such as opioid induced
hyperalgesia and opioid tolerance that accompanies opioid dependency will be thoroughly discussed. Research studies and textbooks were explored in order to explain these phenomena.
INITIAL REVIEW OF LITERATURE

Conducting a thorough literature review was the foundation of my project. The literature revealed the current modalities being used for acute surgical pain treatment for chronic pain patients undergoing general anesthesia. I have reviewed 10 articles at this point in the project, and they are incorporated in the table of evidence (Appendix A).

Modalities used in treating acute surgical pain in chronic opioid dependent patients are the administration of ketamine intraoperatively (Loftus et al., 2010; Urban, Deau, Wukovits, & Lipnitsky, 2008) and the administration of a fentanyl challenge and subsequent infusion intraoperatively (Davis et al., 2003; Davis et al., 2005). Another modality is use of multimodal analgesia (Fu et al., 2010).

Treatment guidelines found in the literature needed to be evaluated and incorporated into any treatment recommendations, as appropriate (Brill, Ginosar, & Davidson, 2006; Carroll, Angst, & Clark, 2004; Dykstra, 2012). In addressing the knowledge gap of healthcare providers about the changes that occur with opioid dependence, evidence was synthesized to explain these changes and how they affect acute pain management (Bajwa, 2012; Harris, 2008; Liang et al., 2008; Painter & Crofford, 2013).

Other evidence used in my project sets the foundation for care delivery. For example, the argument can be made that preoperative pain is a risk factor for chronic post-surgical pain (Gerbershagen et al., 2009). Therefore, it is vital that preoperative pain status is assessed and that intraoperative pain is treated adequately in all patients, including those with chronic opioid dependency. Furthermore, I addressed the issue that chronic opioid dependent patients may have more postoperative pain as compared to
opiate naïve patients (Chapman, Davis, Donaldson, Naylor, & Winchester, 2011; Chapman, Donaldson, Davis, Ericson, & Billharz, 2009; VanDenKerkhof et al., 2012).
METHODS

The methods used in this literature review focused on identifying the different modalities and their efficacy. This section of the paper describes how I collected the evidence in order to connect it to the purpose of my project. In addition, the maintenance of ethical standards will be addressed.

The primary goal of my project was to identify the different modalities (and their efficacy) of acute surgical pain treatment that have been used in chronic opioid dependent patients. The methods used for data collection included an in-depth literature review. Case reports, research studies, and dissertations were reviewed. The population of interest is adults with chronic pain syndromes undergoing surgical procedures with general anesthesia. Excluded was evidence in pediatric, pregnant female, and animal samples, or that describing procedures performed under sedation, or reports written in a language other than English. Since this project was solely extracting information from databases (PubMed, Ovid, Cumulative Index to Nursing and Allied Health Literature) and human participants were not involved, ethical standards were maintained and institutional board review was not sought.

The secondary goal of this project was to discuss the physiologic changes in organ function that occur with opioid dependency as these affect the management of acute surgical pain. Similar to the primary goal, an exhaustive literature review was conducted; research studies and textbooks were explored. However, since the physiology of chronic pain is continuously being researched, human studies and animal studies were included. As above, ethical standards were maintained because human participants were not involved in the project.
RESULTS

In the results section of this paper, I initially describe the evidence that has been collected regarding the current practice recommendations available to healthcare providers for the treatment of acute surgical pain in chronic opioid dependent patients undergoing major surgery with general anesthesia. Then, the efficacy of the medications that are being used for treatment is discussed. The medications under review include multimodal analgesia (with and without ketamine), fentanyl challenge, intravenous (IV) lidocaine, and methadone.

Current Practice Recommendations

A literature search was conducted on PubMed and Cumulative Index to Nursing and Allied Health Literature (CINAHL) in order to evaluate current practice recommendations in treating acute surgical pain during general anesthesia in chronic opioid dependent patients. Major search terms included: “opioid dependent patients,” “opioid tolerant patients,” and “opioid abuse.” Each of these terms was combined with the terms “perioperative pain management,” “acute pain management,” and “postoperative management.” This search yielded two systematic reviews (SRs), one retrospective case control, and nine review articles. Authors of these publications made the following common practice recommendations, which are supported by the sources in the table in Appendix A:

- Administer the patient’s daily regimen of opioid preoperatively (Bourne, 2008; Brill et al., 2006; Carroll et al., 2004; Dykstra, 2012; Kopf, Banzhaf, & Stein, 2005; Lewis & Williams, 2005; Mehta & Langford, 2006; Mitra &
Sinatra, 2004; Rozen & DeGaetano, 2006; Stromer, Michaeli, & Sandner-Kiesling, 2013).

- Initiate multi-modal medications preoperatively (Bourne, 2008; Brill et al., 2006; Carroll et al., 2004; de Leon-Casasola, 1996; Dykstra, 2012; Gordon et al., 2008; Hadi, Morley-Forster, Dain, Horrill, & Moulin, 2006; Kopf et al., 2005; Mehta & Langford, 2006; Mitra & Sinatra, 2004; Stromer et al., 2013).

- A transdermal fentanyl patch may be removed intraoperatively with equi-analgesic IV opioid being administered (Bourne, 2008; Brill et al., 2006; Kopf et al., 2005; Lewis & Williams, 2005; Mehta & Langford, 2006; Mitra & Sinatra, 2004; Rozen & DeGaetano, 2006; Stromer et al., 2013).

- Administer liberal opioids intraoperatively with anticipation of higher opioid requirements (Gordon et al., 2008; Mitra & Sinatra, 2004; Rozen & DeGaetano, 2006).

- Initiate an IV patient-controlled analgesic (PCA) with an opioid postoperatively (Bourne, 2008; Brill et al., 2006; Carroll et al., 2004; Dykstra, 2012; Gordon et al., 2008; Hadi et al., 2006; Lewis & Williams, 2005; Mehta & Langford, 2006; Mitra & Sinatra, 2004; Rozen & DeGaetano, 2006; Stromer et al., 2013).

- In order to avoid opioid withdrawal, the patient-controlled analgesia (PCA) should have an adequate basal rate, which is determined as the equi-analgesic dose of the patient’s oral opioid regimen (Dykstra, 2012; Hadi et al., 2006; Kopf et al., 2005; Lewis & Williams, 2005; Mehta & Langford, 2006; Mitra & Sinatra, 2004; Rozen & DeGaetano, 2006; Stromer et al., 2013). Bolus dose requirements will be
higher than that for opioid naïve patients (Lewis & Williams, 2005; Mehta & Langford, 2006; Mitra & Sinatra, 2004; Stromer et al., 2013).

As seen in Appendix A table, over half of the articles cited a study conducted by Rapp, Ready, and Nessly (1995) as shown in Appendix B. In this retrospective case control study, 180 chronic opioid dependent participants were matched with non-opioid participants on age, gender, type of surgery, and postoperative pain management. Postoperatively, participants received either an epidural with a morphine bolus titrated to analgesic effect, an epidural with bupivacaine 0.0625% and fentanyl 2 mcg/ml, or IV PCA of opioids. Dosage and intervals between doses for IV PCA opioids were titrated to analgesic effect. Results revealed that postoperative median pain scores (verbal pain scores) were higher in the chronic opioid dependent participants at rest and with stimulation as compared to the controls ($p = .0001$). In addition, chronic opioid dependent participants were under the care of acute pain service longer ($p = .0001$) than the controls. Chronic opioid dependent participants also required statistically significant ($p = .0001$) more anxiolysis (18.7%) as compared to controls (0.7%). Interpretation of this data was challenging, as the authors did not present it clearly to the reader. Lastly, it was identified that there is a positive correlation between preoperative and postoperative opioid dosing, $r = .49, p = .04$, among the matched cases and controls (Rapp et al., 1995). This suggests that patients with a higher preoperative opioid dose will receive higher postoperative doses. Therefore, this corroborates the practice recommendation of administering liberal amounts of opioids with the anticipation of higher opioid dose requirements postoperatively in chronic opioid dependent patients versus than opioid naïve patients.
Even though the list of recommendations were mentioned in the literature, the focus of this doctoral project was to identify those pharmacologic agents that have documented efficacy in treating acute pain in chronic opioid dependent patients undergoing major surgery with general anesthesia. Therefore, the following sections of this paper describe the evidence found regarding the following pharmacologic treatment modalities: multimodal analgesia (with and without ketamine), fentanyl challenge, IV lidocaine, and methadone.

**Multimodal Analgesia**

Kehlet (1989) first described multimodal analgesia as a combination of analgesic regimens in order to achieve analgesia. The goal was to provide adequate analgesia while reducing the doses of analgesics and side effects. Currently, multimodal analgesia describes the use of multiple medications and non-drug modalities administered via different routes that act on a variety of receptors or targets in order to obtain beneficial effects (i.e., decrease pain and side effects or both; Joshi, 2005). For example, nonsteroidal anti-inflammatory drugs (NSAIDS), opioids, local anesthetics, and N-Methyl-D-Aspartate (NMDA) antagonists might be used in combination as a multimodal approach in an attempt to alleviate perioperative pain. Similarly, preemptive analgesia strives to alleviate pain. Katz and colleagues (1992) first described preemptive analgesia, a treatment based upon the likelihood that neural blockade via opiates or local anesthetics prior to surgical incision would prevent the central nervous system from developing wind-up or central sensitization (Brown & Fink, 2009; Katz et al., 1992; Kehlet, 1994). However, more recently, the concept of “preventative” analgesia has been implemented.
This consists of multimodal analgesia being implemented in the preoperative area and continued intraoperatively and postoperatively (Brown & Fink, 2009).

A literature search was conducted electronically on PubMed and CINAHL in order to determine the efficacy of multi-modal analgesia in treating acute surgical pain during general anesthesia in chronic opioid dependent patients. Major search terms included: “multi-modal analgesia” and “preemptive analgesia.” Each of these terms was combined with the terms “chronic opioid dependent patients,” “opioid tolerant patients,” and “opioid dependent patients.” Studies that were excluded included surgical procedures that were performed with sedation and those studies where analgesics were administered postoperatively as “rescue” measures for uncontrolled pain. In addition, studies that did not include chronic opioid dependent patients, opioid tolerant patients or those with a history of drug abuse were also excluded. This resulted in 14 articles that were used for analysis. These articles consisted of one observational study, two quasi-experimental studies, six randomized control trials (RCTs), three systematic reviews, and two Cochrane reviews. The efficacy of multimodal analgesia was determined by a statistically significant difference ($p < .05$ as reported by the original investigators) in pain relief, which was measured by consumption of supplementary opioids and/or postoperative pain scores.

Ketamine, an $N$–Methyl-D-Aspartate (NMDA) antagonist, is used alone as an induction agent for anesthesia or in combination with other medications (multimodal) for perioperative pain control. Ketamine blocks the NMDA receptor, thereby preventing its activation. The NMDA receptor has been associated with the development of wind up or central sensitization that occurs with chronic pain (Bordi, 2014). Commonalities within
the studies include the use of ketamine as part of a multi modal regimen (Loftus et al., 2010; Mathiesen et al., 2013; Pacreu, Candil, Molto, Carazo, & Galinski, 2012; Sharma, Balireddy, Vorenkamp, & Durieux, 2012; Subramaniam et al., 2011; Yuan-Yi, Kang, Yuan-Chin, Huang-Chou, & Chich-Shung, 1998). In a Cochrane review, as seen in Appendix C, authors reported that ketamine decreased morphine PCA consumption in the first 24 hours postoperatively in 11 of 37 RCTs; from a meta-analysis using findings from these 11, they reported a decreased morphine PCA consumption during the first 24 hours postoperatively of -15.96 mg, 95% CI [-19.69, -12.24] (Bell, Dahl, Moore, & Kalso, 2010). In addition, 27 of 37 RCTs revealed that ketamine also decreased postoperative nausea and vomiting (PONV; p = .001). Chronic opioid dependent patients were not excluded in this study and can be assumed as part of the sample.

As seen in Appendix D, almost half of the 14 articles evaluated in this project revealed significant decreases in post-operative opioid consumption (B. Lee et al., 2013; Loftus et al., 2010; Mathiesen et al., 2013; Pacreu et al., 2012; Rajpal et al., 2010; Yuan-Yi et al., 1998). Of these, two used multimodal analgesia without ketamine as an adjunct (B. Lee et al., 2013; Rajpal et al., 2010).

In those studies where ketamine was used as an adjunct, a decrease in postoperative pain scores was noted in two studies (Loftus et al., 2010; Yuan-Yi et al., 1998). Loftus et al. (2010) determined that ketamine was effective in decreasing opioid consumption in chronic opioid dependent patients undergoing major lumbar spine surgery. Those (n = 52) who received a ketamine bolus with an infusion intraoperatively had a statistically significant decrease (p < .05) in opioid consumption at 48 hours postoperatively compared to those (n = 50) who received a placebo. However,
postoperative pain scores (visual analogue scale [VAS]) were equivalent in both groups 
(Loftus et al., 2010). Unlike Loftus et al. (2010), a study conducted by Urban et al. 
(2008) established that low dose ketamine infusion intraoperatively in chronic opioid 
dependent patients receiving posterior lumbar fusion surgery, decreased postoperative 
pain (self-reported). However, opioid consumption was not decreased. The participants 
(n = 24) were randomly assigned to receive an intraoperative ketamine bolus of 0.2mg/kg 
followed by an infusion of 2 mcg/kg/hr (n = 12) or to act as a control (n = 12). Both 
groups received IV PCA of hydromorphone postoperatively. There was a statistically 
significant decrease (p < .05) in postoperative pain in the postanesthesia care unit 
(PACU) and on the first postoperative day in the experimental group. 

In contrast to Loftus et al. (2010) and Urban et al. (2008) where ketamine was 
used intraoperatively, Yuan-Yi et al. (1998) examined the efficacy of ketamine via 
edpidural administration post surgically. All 91 participants undergoing major 
intrathoracic or upper abdominal surgery received an infusion at 2.5 ml/hr of morphine 
0.02 mg/ml, 0.08% bupivacaine and epinephrine (1:250,000) 4 mcg/ml via epidural prior 
at the end of surgery. However, the experimental group (n = 45) received the addition of 
ketamine 0.4 mg/ml via epidural. There was a statistically significant increase (p < .05) 
in VAS scores with movement on the third postoperative day and at rest on the second 
postoperative day in the control group. In addition, there was a statistically significant 
increase (p < .05) in opioid use the first two days postoperatively in the control group. 
Therefore, adding ketamine epidurally decreased opioid consumption and improved 
analgesia postoperatively. Nevertheless, the study authors did not disclose if chronic
opioid dependent patients were included in the sample and are assumed to have been included.

**Fentanyl Challenge**

Fentanyl is a synthetic phenylpiperidine opioid agonist that is 75-100 times more potent than morphine (Griffin & Woolf, 2008). It is highly lipophilic which accounts for its short duration of action (approximately 20-40 minutes) after administering a single intravenous dose (Nagelhout, 2014b). Due to fentanyl's short duration of action and lack of active metabolites, it is the most commonly used opioid in anesthesia for treating acute surgical pain.

Several practice recommendations supported the use of a “fentanyl challenge” in estimating opioid requirements in chronic opioid dependent patients undergoing major surgery (Brill et al., 2006; Rozen & DeGaetano, 2006). In order to determine its efficacy, an electronic literature search via PubMed and CINAHL was conducted. The major search term used was “fentanyl challenge.” This term was combined with the terms “chronic opioid dependent patients,” “opioid tolerant patients,” and “opioid dependent patients.” This resulted in two articles, one quasi-experimental study and a case report that were used for analysis as seen in Appendix E.

Davis et al. (2005) conducted a quasi-experimental study with 19 chronic opioid dependent patients undergoing multilevel spine fusion surgery. Prior to the induction of general anesthesia, all participants received a fentanyl infusion of 2mcg/kg/min until the respiratory rate was less than five breaths per minute. Pharmacokinetic simulation software determined the fentanyl effect-site concentration (Ce) at the onset of respiratory depression. A fentanyl infusion rate was established to provide a Ce at a rate 30% of that
associated with respiratory depression (Davis et al., 2005). The fentanyl infusion rate was continued intraoperatively and in the post anesthesia care unit. Thereafter, an IV PCA basal infusion was set at 50% of the predicted hourly requirement. In addition, the PCA was adjusted to allow the patient to achieve two to three demand doses per hour. Fentanyl plasma levels were drawn at steady-state PCA settings. There was a statistically significant correlation \( (p < .00001) \) of plasma fentanyl levels and the Ce associated with respiratory depression. In addition, all but one patient required increases in the PCA postoperatively and none required interventions to breath.

Similarly, in a case report of a chronic opioid dependent patient undergoing repeat tricuspid valve replacement surgery, a fentanyl challenge was initiated prior to anesthesia to determine intraoperative and postoperative analgesic requirements (Davis et al., 2003). A fentanyl infusion of 2mcg/kg/min was administered for 80 minutes without respiratory depression or unresponsiveness. The infusion was increased to 40 mcg/kg/min that resulted in patient unresponsiveness. Pharmacokinetic software determined the fentanyl Ce at the time of unresponsiveness. Postoperatively, a fentanyl infusion via PCA was started at 25% of the fentanyl Ce at the time of unresponsiveness. The patient reported satisfaction with the analgesia provided. Furthermore, there was no incidence of respiratory depression or side effects warranting intervention.

**Lidocaine**

When peripheral tissues are injured via thermal, mechanical, or chemical stimuli, an inflammatory response occurs. This inflammatory response is responsible for the release of proinflammatory cytokines such as interleukin-1β (IL-1β), tumor necrosis
factor (TNF), and interleukin-6 that can sensitize neurons and lead to hyperalgesia (Bordi, 2014; A. Clark, Old, & Malcangio, 2013; Üceyler, Schäfers, & Sommer, 2009).

Lidocaine, an amide local anesthetic, possesses anti-inflammatory and analgesic properties. It exerts its effect peripherally and centrally. Lidocaine’s analgesic effect is primarily due to blockade of the sodium channels thereby inhibiting neuronal transmission at the site of injury (Nagelhout, 2014a). In an animal study, it was found that lidocaine decreases nociceptive responses in the dorsal horn of the spinal cord (Jaffe & Rowe, 1995). Lidocaine also reduces the in vitro release of cytokines, resulting in decreased leukocyte actions and its anti-inflammatory effect (Sinclair, Eriksson, Gretzer, Cassuto, & Thomsen, 1993).

A literature search was conducted electronically on PubMed and CINAHL in order to determine the efficacy of IV lidocaine in treating acute surgical pain during general anesthesia in chronic opioid dependent patients. Major search terms included: “perioperative lidocaine” and “intraoperative lidocaine.” Each of these was combined with the terms “postoperative analgesia” and “postoperative pain.” Studies that were excluded included surgical procedures that were performed with sedation, and those where lidocaine was by non-intravenous routes or administered solely postoperatively. In addition, studies that did not include chronic opioid dependent patients, opioid tolerant patients or those with a history of drug abuse were also excluded. This resulted in five articles (three meta-analyses and two RCTs) for analysis. The efficacy of IV lidocaine was determined by a statistically significant difference (p < .05 as reported by the original investigators) in pain relief, which was measured by consumption of supplementary opioids and/or postoperative pain scores. All studies revealed decreased
postoperative pain scores with perioperative IV lidocaine as seen in Appendices F and G (Farag et al., 2013; Kim et al., 2013; Marret, Rolin, Beausssier, & Bonnet, 2008; Sun, Li, Wang, Yun, & Gan, 2012; Vigneault et al., 2011).

The efficacy of IV lidocaine in patients undergoing abdominal surgeries was evaluated in two meta-analyses (Marret et al., 2008; Sun et al., 2012). Sun et al. (2012) reviewed 21 RCTs where systemic lidocaine was compared with placebo. Of these, 17 studies initiated IV lidocaine preoperatively with a bolus of 100 mg or 1.5-2 mg/kg/hr. Thereafter, an infusion was started at 1.5-3 mg/min until the end of surgery or 1, 4, or 24 hours postoperatively. Systemic lidocaine significantly decreased pain intensity scores (VAS) in 11 RCTs at 6 hours postoperatively at rest, -8.07 mm, 95% CI [-14.69, -1.49], and during activity, -10.56 mm, 95% CI [-16.89, -4.23]. Likewise, in 13 RCTS, IV lidocaine significantly decreased pain scores at 24 hours postoperatively at rest, -4.41 mm, 95% CI [-7.71, -1.13], and during activity in 9 RCTs, -4.04 mm, 95% CI [-8.00, -0.09]. Data from 14 RCTs also revealed that postoperative opioid consumption (from the end of surgery to 48 hours after surgery) was reduced in the lidocaine groups as compared to placebo, -7.04 mg, 95% CI [-10.40, -3.68]. Since it was not disclosed if chronic opioid dependent patients were included in the sample, it is assumed that they were. In addition, there was a lack of homogeneity among the abdominal surgeries (e.g., laparoscopic vs. open) and the surgical extensiveness (e.g., cholecystectomy vs. abdominal hysterectomy).

Similarly, Marret et al. (2008) reviewed eight RCTs (six of these excluded chronic opioid dependent patients) where IV lidocaine was administered and compared with placebo in patients undergoing abdominal surgeries. In seven of these, patients received a 1.5 mg/kg lidocaine bolus prior to surgical incision with a subsequent infusion started
from 1 hour to 24 hours after incision closure. There were significantly decreased postoperative pain scores (VAS) in six RCTs at 24 hours in the lidocaine groups as compared to placebo, -5.93 mm, 95% CI [-9.63, -2.23]; \( p = .002 \). However, a subgroup analysis was not performed to determine if chronic opioid dependent patients were included. In addition, Marret et al. did not reveal information regarding opioid consumption. Compared to Sun et al. (2012), Marret et al. also lacked homogeneity in terms of abdominal surgery types and extensiveness.

Unlike Marret et al. (2008) and Sun et al. (2012), Vigneault et al. (2011) reviewed the efficacy of IV lidocaine during general anesthesia in all types of surgical procedures. Their review included 29 RCTs that used IV lidocaine in comparison to placebo or any comparator. Results from nine studies revealed that at 6 hours postoperatively, IV lidocaine reduced pain scores (VAS) at rest, -8.70 mm, 95% CI [-16.19, -1.21], during cough (nine studies), -11.19, 95% CI [-17.73, -4.65], and during movement (two studies), -9.56, 95% CI [-17.31, -1.80]. Postoperative pain scores at 12 hours were reduced in the lidocaine groups at rest (6 studies), -6.52 mm, 95% CI [-12.2, -0.91], and during cough (4 studies), -7.44 mm, 95% CI [-14.24, -0.63]. In addition, pain control during cough were/was statistically significant in the lidocaine groups as compared to the placebo at 24 hours (six studies), -6.94 mm, 95% CI [-12.87, -1.01]. Those studies where there were significant reductions in pain scores at 6, 12, and 24 hours postoperatively with cough were mainly in abdominal surgeries (Vigneault et al., 2011). However, there was no significant reduction in pain scores postoperatively during movement with abdominal surgeries (Vigneault et al., 2011).
Lastly, opioid consumption was significantly reduced in the IV lidocaine group (12 studies) as compared to the control group, -8.44 mg, 95% CI [-11.32, -5.56], which was in patients undergoing abdominal surgeries. In addition, it was not disclosed if chronic opioid dependent patients were included in the studies.

Unlike the meta-analyses that included patients undergoing abdominal surgeries, an RCT evaluated the efficacy of IV lidocaine in patients undergoing multilevel spine surgery. Farag et al. (2013) randomly assigned 57 participants to receive, prior to induction of general anesthesia, an IV lidocaine infusion of 2mg/kg/hr until discharge from the post anesthesia care unit or 8 hours. The control group (n = 58) received equal volume of normal saline. Of the sample participants, 28 were opioid dependent (19 in control, 9 in experimental group). Results revealed that those who received IV lidocaine had less subjective pain (p < .001), adjusted mean scores 4.4 mm, 95% CI [4.2, 4.7], as compared to placebo, 5.3 mm, 95% CI [5.0, 5.5]. However, no superiority on 48-hour postoperative morphine consumption was found in the lidocaine group (Farag et al., 2013). In addition, there was no subgroup analysis performed on those participants who were opioid dependent.

A second RCT that assessed the efficacy of IV lidocaine in early gastric cancer patients undergoing laparoscopic-assisted distal gastrectomy surgery, also revealed an improvement in pain scores (VAS) postoperatively (Kim et al., 2013). In this study, 17 participants received an IV bolus of 1.5 mg/kg of lidocaine followed by an infusion of 2 mg/kg/hr intraoperatively. The control group (n = 17) received an equal volume of normal saline. Both groups received a fentanyl IV PCA postoperatively. Pain scores at 2, 4, 8, 12 and 24 hours were significantly decreased along with total opioid consumption.
(p < .05) in the lidocaine group as compared to the placebo. However, Kim et al. (2013) did not disclose if chronic opioid dependent patients were included in their sample; therefore, it is assumed that they were.

**Methadone**

Methadone is a highly lipophilic synthetic opioid that consists of two enantiomers, d-isomer and l-isomer. Its analgesic effects are primarily due to the l-isomer that acts as a mu receptor agonist. The d-isomer is responsible for inhibiting the reuptake of norepinephrine and serotonin, as well as antagonizing the NMDA receptor. Therefore, the d-isomer is attributed to methadone’s anti-hyperalgesic effect and its ability to prevent opioid tolerance (Bordi, 2014; Chung, 2011). Methadone’s high lipophilic profile results in a long half-life (15-60 hours) with variable pharmacokinetics making dosing challenging (Bordi, 2014). Methadone is primarily used for opioid detoxification but is also used for chronic and intraoperative pain management.

A literature search was conducted electronically on PubMed and CINAHL in order to determine the efficacy of intraoperative methadone in treating acute surgical pain during general anesthesia in chronic opioid dependent patients. Major search terms included: “intraoperative methadone” and “perioperative methadone.” Each of these terms was combined with the terms “postoperative analgesia” and “postoperative pain.” Excluded were studies with surgical procedures that were performed with sedation, methadone was used in a maintenance program for opioid detoxification, methadone was used as a “rescue” analgesic, samples with pregnant females, and exclusion of chronic opioid dependent patients, opioid tolerant patients or those with a history of drug abuse.
Ten articles were found but all were excluded for this project due to including at least one of the exclusion criteria.

**Summary**

Overall, an in-depth literature review was conducted which revealed the current practice recommendations for treating acute pain in chronic opioid dependent patients undergoing major surgery under general anesthesia. In addition, the empirical evidence regarding the different medicinal modalities and their efficacies used to treat these patients was also presented. Based on the results of the literature review, implications to practice will be discussed.
DISCUSSION

Anesthesia providers continue to be confronted with the challenges of providing effective analgesia for chronic opioid dependent patients who undergo major surgery with general anesthesia. Several important questions were addressed in this project:

1. What are the current practice recommendations and are they evidence-based?
2. What medications, based on empirical evidence, are efficacious in treating acute surgical pain in CODPs undergoing major surgery with general anesthesia?

The primary means of addressing these questions was to conduct a thorough literature review on (a) current practice guidelines, and (b) the efficacy of different modalities of acute pain relief in chronic opioid dependent patients undergoing major surgical procedures. Medications that were included in the literature review included fentanyl challenge, multi modal analgesia (with and without ketamine), IV lidocaine, and methadone. In addition, the secondary objective was to suggest treatment recommendations for acute pain management for chronic opioid dependent patients based upon the literature review and expert opinion.

The clinical implications of inadequate treatment of acute surgical pain in chronic opioid dependent patients include longer hospital stays, increased financial costs, and patient dissatisfaction. In addition, health care providers are challenged with identifying chronic opioid dependent patients who may be ingesting opioids that are not prescribed for chronic pain syndromes or are illicit opioid abusers. Healthcare providers query patients regarding their medications, specifically opioids, and illicit drug use. However, some patients are not forthright. Therefore, a thorough preoperative assessment is critical
in identifying chronic opioid dependent patients. Given the growing development and use of electronic health records (EHR), one way to screen patients for pre-operative opioid usage would be an EHR query. The EHR would also be beneficial in collecting data and trends of opioid use and dosing in a work setting. Therefore, it is recommended in future studies that EHRs be considered a potential source of obtaining data in this patient population.

The current practice recommendations consist of citations from secondary sources, review articles, studies where chronic opioid dependent patients were excluded, and personal/expert opinion based on clinical practice as shown in Appendix B. One exception is sources that cite Rapp et al. (1995), who did a retrospective case study. Rapp et al. described the postoperative pain management in 180 chronic pain and opioid dependent patients as compared with the matched controls of non-opioid dependent patients where, postoperatively, patients received either an epidural with a morphine bolus, an epidural with bupivacaine and fentanyl or IV PCA with an opioid. They found that opioid dependent patients had significantly greater postoperative pain levels that required significantly more postoperative opioids and anxiolytics than did controls (Rapp et al., 1995). However, opioid dependent patients had fewer opioid side effects than did the controls, which may be due to opioid tolerance. This established a definite problem in alleviating acute surgical pain in chronic opioid dependent patients. Since this was a retrospective study, and data were challenging to interpret, a replication of this study is highly recommended. Perhaps with more control of confounding variables and more transparency of sample demographics and detail related to chronicity of opioid
dependence, such a study might lead to important findings with important patient care implications. Even so, the guideline literature reviewed supports four recommendations:

1. The administration of escalating doses of opioids is necessary in order to achieve an analgesic effect due to opioid tolerance.

2. Avoiding opioid withdrawal is paramount.

3. Patients should be administered their preoperative daily opioid dosage regardless of surgery.

4. Patients should not be given opioid antagonists.

Patients with increased preoperative pain are more likely to have increased postsurgical pain. Knowing this, anesthesia providers must strive to provide effective analgesic medications for chronic opioid dependent patients intraoperatively. Based on the evidence found in this literature review regarding multi modal analgesia (with and without ketamine), fentanyl challenge, IV lidocaine, and methadone, implications are as follows:

1. Decreased opioid consumption postoperatively was found with ketamine as an adjunct in a multi modal regimen. Supporting this, in two RCTs where IV ketamine was used as an adjunct intraoperatively for chronic opioid dependent patients undergoing major spine surgery, a decrease in opioid consumption postoperatively (Loftus et al., 2010) and a decrease in postoperative pain (Urban et al., 2008) were found. In addition, a recent Cochrane review corroborated decreased postoperative opioid consumption with adjunctive ketamine (Bell et al., 2010). It is assumed that chronic opioid dependent patients were included in the sample. Therefore, extrapolating from these data
Intraoperative administration of ketamine as an adjuvant analgesic modality may be effective in enhancing intraoperative and postoperative analgesia for chronic opioid dependent patients undergoing major surgery.

2. The use of a fentanyl challenge as an analgesic modality is promising in assisting anesthesia providers with dosing opioids intraoperatively for chronic opioid dependent patients. A disadvantage to the fentanyl challenge is that it requires the appropriate pharmacokinetic simulation software and a significant amount of time in titrating fentanyl incrementally with a desired respiratory depression rate. Therefore, the practicality of its use is unlikely in the daily surgical setting.

3. The results for IV lidocaine were overwhelmingly favorable for decreasing postoperative pain scores and opioid consumption in patients undergoing abdominal surgeries (Marret et al., 2008; Sun et al., 2012). However, there was a lack of homogeneity in type and extensiveness of the abdominal surgeries. In addition, Marret et al. (2008) failed to perform a subgroup analysis for chronic opioid dependent patients. Likewise, Sun et al. (2012) did not report whether chronic opioid dependent patients were excluded in their sample and were assumed as being included. The practicality of this clinical practice must be determined for each patient and procedure.

4. It is recommended that further research be conducted with the use of methadone as an adjunctive analgesic for alleviating acute surgical pain in chronic opioid dependent patients. Currently, research is aimed at opioid
dependent parturients and in treating acute surgical pain in opioid naïve patients. Since methadone exhibits anti-hyperalgesic and analgesic properties, implementation of methadone in chronic opioid dependent patients undergoing major surgery may be beneficial in decreasing opioid consumption and postoperative pain.

Overall, this literature review helps to further define the current state of knowledge and the treatment options for chronic opioid dependent patients undergoing major surgery. Of the medications included in this literature review, ketamine, as part of a multi-modal regimen, and IV lidocaine (when given during abdominal surgeries) are the most promising. However, further research that includes chronic opioid dependent patients is recommended.
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### APPENDIX A

**PRACTICE RECOMMENDATIONS COMPARISONS**

Comparisons of Practice Recommendations for Perioperative Acute Pain Management in Chronic Opioid Dependent Patients

<table>
<thead>
<tr>
<th>Author(s) Year</th>
<th>Ketamine</th>
<th>Fentanyl challenge</th>
<th>Multi-modal</th>
<th>Opioid dosing intraop</th>
<th>Methadone</th>
<th>Fentanyl patch</th>
<th>Postop opioid dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bourne, 2008 (SR)</td>
<td>N</td>
<td>N</td>
<td>Y-CI</td>
<td>Y-C Mitra &amp; Sinatra; Lewis &amp; Williams-differences in expert opinions</td>
<td>N</td>
<td>Y-C Mehta &amp; Langford (which cited Mitra &amp; Sinatra) leave on intraop = not what Mitra reports = CI</td>
<td>Y-cited Mitra &amp; Sinatra, Lewis &amp; Williams &amp; Mehta &amp; Langford = varying PCA recommendations based on expert opinion; All the above authors agree that C- Rapp et al = ↑ opioid dose: ↑ ↑ PCA dose</td>
</tr>
<tr>
<td>Carroll et al., 2004 (R)</td>
<td>Y-cited from studies that used ketamine postop; CODPs excluded.</td>
<td>N</td>
<td>Y-NC for CODPs</td>
<td>Y-CI Rapp et al. &amp; de Leon</td>
<td>N</td>
<td>N</td>
<td>Y-C Rapp et al.; personal recommendations in their institution</td>
</tr>
<tr>
<td>de Leon-Casasola, 1996 (R)</td>
<td>N</td>
<td>N</td>
<td>Y-NC</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Dykstra, 2012 (SR)</td>
<td>N</td>
<td>N</td>
<td>Y-NC</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y-C-Rapp et al.</td>
</tr>
<tr>
<td>Author(s) Year</td>
<td>Ketamine</td>
<td>Fentanyl challenge</td>
<td>Multi-modal</td>
<td>Opioid dosing intraop</td>
<td>Methadone</td>
<td>Fentanyl patch</td>
<td>Postop opioid dose</td>
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</tr>
<tr>
<td>Gordon et al., 2008</td>
<td>Y-C Carroll et al. (R)</td>
<td>N</td>
<td>Y-NC</td>
<td>N</td>
<td>N</td>
<td>Y-C Rapp et al.</td>
<td></td>
</tr>
<tr>
<td>Hadi et al., 2006 (R)</td>
<td>Y-C- Eilers et al.; Sator-Katzenschlager et al. (CR) = for postop pain.</td>
<td>N</td>
<td>Y-NC</td>
<td>Y-NC</td>
<td>N</td>
<td>N</td>
<td>Y-PCA-NC personal experience</td>
</tr>
<tr>
<td>Kopf et al., 2005 (R)</td>
<td>Y-for postop pain-C-Duncan (CR)</td>
<td>N</td>
<td>Y-NC</td>
<td>Y-C Rapp et al.</td>
<td>N</td>
<td>Y-NC</td>
<td>N</td>
</tr>
<tr>
<td>Lewis &amp; Williams, 2005 (R)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y-C de Leon</td>
<td>N</td>
<td>Y-remove intraop “per manufacturer”</td>
<td>Y-NC</td>
</tr>
<tr>
<td>Rozen &amp; DeGaetano, 2006 (R)</td>
<td>N</td>
<td>Y-C-Davis, Johnson et al. (CR)</td>
<td>N</td>
<td>Y-C Weinrieb at al.; Rapp et al.</td>
<td>N</td>
<td>Y-NC no clear guide as to keep on or remove</td>
<td>Y-NC-PCA</td>
</tr>
<tr>
<td>Stromer et al., 2013 (R)</td>
<td>Y-C-Haller (CR)</td>
<td>N</td>
<td>Y-NC</td>
<td>Y-NC</td>
<td>N</td>
<td>Y-NC Avoid withdrawal sx; higher doses of opioids intraop; IV PCA w background infusion</td>
<td>Y-PCA inaccurate from source citation</td>
</tr>
</tbody>
</table>

Note. CODPs = chronic opioid dependent patients; postop = postoperative; preop = preoperative; intraop = intraoperative; periop = perioperative; ↓ = lower/decreased; ↑ = increased/higher; PCA = patient controlled analgesia; Y = yes; N = no; C = cited; NC = not cited; IV = intravenous; sx = symptoms; SR = systematic review; R = review; CR = case report; QE = quasi-experimental; CI = cited inaccurately; w = with.
APPENDIX B

TABLE OF EVIDENCE FOR PRACTICE RECOMMENDATIONS

*Practice Recommendations for Perioperative Acute Pain Management in Chronic Opioid Dependent Patients*

<table>
<thead>
<tr>
<th>Purpose</th>
<th>Design/Variables</th>
<th>Sample/Setting</th>
<th>Measurements</th>
<th>Results</th>
<th>Conclusions; Limitations</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consider literature on treating acute pain in CODPs; audit practice groups regarding pain mgmt. in CODPs (Bourne, 2008)</td>
<td>SR; Questionnaires to 23 hospitals (10 responded)</td>
<td>2 review articles (Rapp et al.; Lewis &amp; Williams) 1 case-controlled retrospective review (Mehta &amp; Langford); 10 respondents</td>
<td>Frequencies used</td>
<td>↑ MS requirements; require ↑ opioid doses postop; preop opioid should be continued; additional analgesia as needed; Questionnaires-9 had a regular practice for CODPs, all had protocol for CODP ca pts but none for CODP non ca pts; 9 do not stop regular opioid while on PCA; inconsistencies with opioid conversions</td>
<td>Focus on case reports, personal experience, expert opinion; no operational definition for “regular practice”</td>
<td></td>
</tr>
<tr>
<td>Discuss perioperative pain management options for CODPs (Brill et al., 2006)</td>
<td>R</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strategies for perioperative analgesia in CODPs (Carroll et al., 2004)</td>
<td>R</td>
<td>N/A-expert opinion</td>
<td></td>
<td>C = Rapp et al.; de Leon-Casasola</td>
<td>Switching pts back to an oral opioid regimen = “works at their institution”; expert opinion</td>
<td></td>
</tr>
<tr>
<td>Protocols from an Acute Pain</td>
<td>R</td>
<td>N/A-expert opinion</td>
<td></td>
<td>For postop pain control</td>
<td>“Large doses of IV opioids and NSAIDS”</td>
<td></td>
</tr>
<tr>
<td>Purpose</td>
<td>Design/Variables</td>
<td>Sample/Setting</td>
<td>Measurements</td>
<td>Results</td>
<td>Conclusions; Limitations</td>
<td>Notes</td>
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<tr>
<td>Service in Buffalo, NY (de Leon-Casasola, 1996)</td>
<td>Implement an evidence-based practice project for periop pain mgmt. in CODPs (Dykstra 2012)</td>
<td>SR-non research levels IV and V</td>
<td>C = Carroll et al.; Mitra &amp; Sinatra; Rapp et al.; Kopf et al.; Rozen &amp; DeGaetano</td>
<td>“Evidence-based recommendation”-basal PCA, multi-modal analgesia BUT NC of the evidence supporting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Gordon et al., 2008)</td>
<td>(Gordon et al., 2008)</td>
<td>CR &amp; expert opinion</td>
<td>C = Carroll et al; Rapp et al.</td>
<td>Treat preop pain in order to ↓ postop pain; COPD have ↑ opioid requirements; Recommend intraop K</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Update on managing CODPs periop. (Hadi et al., 2006)</td>
<td>Update on managing CODPs periop. (Hadi et al., 2006)</td>
<td>R</td>
<td>C = Mitra &amp; Sinatra, de Leon-Casasola;</td>
<td>K intraop –3 supporting citations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Kopf et al., 2005)</td>
<td>(Kopf et al., 2005)</td>
<td></td>
<td>C = de Leon-Casasola; Rapp et al.</td>
<td>↑ dose of opioid required; ↑ PCA dose required</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Lewis &amp; Williams, 2005)</td>
<td>(Lewis &amp; Williams, 2005)</td>
<td>R</td>
<td>C = Rapp et al.; another author w expert opinion</td>
<td>Uses expert opinion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Mehta &amp; Langford, 2006)</td>
<td>(Mehta &amp; Langford, 2006)</td>
<td>R</td>
<td>C = Rapp et al.; Mitra &amp; Sinatra</td>
<td>↑ PCA dose required; expert opinion for recommendation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Mitra &amp; Sinatra, 2004)</td>
<td>(Mitra &amp; Sinatra, 2004)</td>
<td>R</td>
<td>C = review articles; textbooks</td>
<td>Dosing recommendations for periop. analgesia- several disclaimers that the information is from</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Purpose</td>
<td>Design/Variables</td>
<td>Sample/Setting</td>
<td>Measurements</td>
<td>Results</td>
<td>Conclusions; Limitations</td>
<td>Notes</td>
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<tr>
<td>Describe the postop course of CODPs (Rapp et al., 1995)</td>
<td>Retrospective case control; DV = CODPs Matched for age, gender, type of surgery, postop pain treatment</td>
<td>180 control pairs; surgery within 6 months, type of surgery, gender, type of pain relief (epidural or PCA)</td>
<td>Pruritus, N/V, sedation, GU retention = absent, mild, moderate, severe; Pain = VRS; Anxiolysis = midazolam/lorazepam</td>
<td>$p = 0.0001$-postop CODPs had ↑ pain scores at rest and with stimulation; $p = 0.0001$-postop CODPs required acute pain service longer; CODPs required ↑ epidural doses; ↑ N/V, pruritus, GU retention in controls</td>
<td>CODPs require ↑ doses of opioids postop; OPDs require ↑ anxiolytics; CODPs have tolerance to SE of opioids</td>
<td>Case control study to identify ↑ postop opioid dose requirements for CODPs versus controls. Useful to cite the CODPs have ↑ requirements for dosing. Limitations-the 2 groups are not totally comparable/homogeneity is questionable; no randomization; no control for intraop course of medications given.</td>
</tr>
<tr>
<td>Discuss impact of CODPs and anesthetic management (Rozen &amp; DeGaetano, 2006)</td>
<td>R</td>
<td></td>
<td></td>
<td>C = Weinrieb et al. = MMT liver transplant pts have ↑ requirements for dosing; Davis et al. = fentanyl challenge for dosing intraop</td>
<td>Useful to cite the CODPs have ↑ requirements for dosing.</td>
<td></td>
</tr>
<tr>
<td>periop. tx. for opioid addicted pts (Stromer et al., 2013)</td>
<td>R</td>
<td></td>
<td></td>
<td>C = Mitra et al.; Rapp et al.; de Leon-Casasola; Carroll et al.; Himmelseher et al.</td>
<td>Avoid withdrawal sx; ↑ doses of opioids intraop; K intraop; IV PCA w background infusion</td>
<td></td>
</tr>
</tbody>
</table>

Note. CODPs = chronic opioid dependent patients; postop = postoperative; preop = preoperative; intraop = intraoperative; periop = perioperative; ↓ = lower/decreased; ↑ = increased/higher; PCA = patient controlled analgesia; tx = treatment N/V = nausea and vomiting; GU = urinary; pts = patients; IV =
intravenous; VRS = verbal rating scale; sx = symptoms; N/A = not applicable; SR = systematic review; R = review; CR = case report; w = with; MS = morphine;
F = fentanyl; DV = dependent variable; NSAIDS = non-steroidal anti-inflammatory drugs; ca = cancer; K = ketamine.
### APPENDIX C

#### TABLE OF EVIDENCE OF SYSTEMATIC REVIEWS FOR MULTIMODAL ANALGESIA

**Systematic Reviews of Multi-Modal Analgesia as a Perioperative Acute Pain Management Modality in Chronic Opioid Dependent Patients Undergoing Surgery Requiring General Anesthesia**

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<tr>
<th>Purpose</th>
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<th>Sample/Setting</th>
<th>Measurements</th>
<th>Results</th>
<th>Conclusions; Limitations</th>
<th>Notes</th>
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</thead>
<tbody>
<tr>
<td>Determine efficacy of K in ca pts. (Bell et al., 2012)</td>
<td>Cochrane Review; 2 RCTs with CODPs w ca receiving either K or placebo.</td>
<td>2 RCTs</td>
<td>Insufficient evidence; no conclusions made</td>
<td># of participants too small (30); Further studies needed</td>
<td>Nothing significant found</td>
<td></td>
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<tr>
<td>Review RCTs from 1996-2010; identify types of surgeries &amp; pts that benefit from periop IV K (Laskowski et al., 2011)</td>
<td>SR; RCTs w placebo as C; IV K only; PRISMA</td>
<td>47 RCTs</td>
<td>Pt age, type of surgery, dose of K, timing of administration, intraop narcotic, postop OC; pain scores = qualitatively</td>
<td>IV K is beneficial in major abd. &amp; thoracic surgeries for postop analgesia; it is effective in ↓ OC &amp; delaying time to first analgesic</td>
<td>No explicit exclusion of CODPs—assume they are included; ↓ OC</td>
<td></td>
</tr>
<tr>
<td>Review RCTs before 2011 &amp; compare therapy for postop pain in pts undergoing spine surgery; find the best pain tx; OVID, MEDLINE, MD consult databases (Sharma et al., 2011)</td>
<td>SR; Trials reporting postop pain scores, &amp;/or OC in pts undergoing spine surgery</td>
<td>82 articles used in review; RCTs-25 NSAIDS, 43 neuraxial, 6 gabapentins, 8 NMDA antagonists</td>
<td>Reported: # pts, type of surgery, type, dose &amp; route of drugs, analgesia outcome measures, cumulative OC, adverse effects of drugs; Pain-2, 24, &amp; 48 hrs postop; cumulative OC @ 24 &amp; 48 hrs; adverse effects only if NSAIDS; pain scores at 2 hrs postop—3 of 10 found sign. Pain relief w; 24 hrs postop pain-13 of 21 sign. Pain relief; conflicting results w 1 or combo NSAIDS; conflicting doses w 48 hrs postop pain relief w NSAIDS; 13 trials analyzed</td>
<td>Overall lack of evidence supporting use of regional, gabapentinois &amp; most NSAIDS; Overall benefit-K, parecoxib, and combo paracetamol &amp; ketoprofen, opioids or NSAIDS</td>
<td>Spine pts Cites Urban et al. &amp; Loftus et al.</td>
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<td>Purpose</td>
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<tr>
<td>Efficacy &amp; safety of low dose K to periop opioid analgesia (Subramaniam et al., 2004)</td>
<td>SR of RCTs double blinded</td>
<td>IV K single dose (11), infusion K w IV opioids (11), PCA w K &amp; MS (6), IV K continuous w epidural opioids (8)</td>
<td>Pain = VAS; side effects; total supplemental analgesic requirements</td>
<td>No ↓ opioid side effects w use of K found; ↓ opioid sparing effect; IV PCA w K &amp; MS did not improve analgesia as compared to MS</td>
<td>K should be considered as an adjuvant in pts with ↑ opioid requirements; unsure if CODPs are included in these studies; variety of surgical procedures</td>
<td>Assuming that CODPs are included</td>
</tr>
<tr>
<td>Evaluate effectiveness in periop K (Bell et al., 2010)</td>
<td>Cochrane Review; RCTs (37) of pts. treated w K or placebo periop</td>
<td>37 RCTs; periop K vs. Cs</td>
<td>In 11 studies w 432 participants, K ↓ PCA MS consumption the 1st 24 hrs post op; WMD = -15.98 mg, w 95% CI [-19.69, -12.24]; 27 of 37 trials found that K ↓ PONV (p = .001)</td>
<td>K ↓ MS consumption the 1st 24 hrs postop and ↓ PONV</td>
<td>Limitations: no definitive dose range for K</td>
<td>No explicit exclusion criteria for CODPs—assume they are included ↓ OC w K</td>
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<td>cumulative OC w NSAIDS 24 hrs postop-only 6 reported ↓ OC; rescue @ 48 hrs = 4 found ↓ OC; K or ME or dextromethorphan = 8 trials-2 w CODPs &amp; K reported that K ↓ immediate postop pain; Gabapentin-6 trials-2 preemptive/2 preop &amp; postop; 2 trials w pain relief @ 24 hrs, others reported no benefit; 24 hrs postop OC ↓ in 4 trials</td>
<td>LAs in CE or single shot steroids/clonidine</td>
<td>Limitations: differences in doses, timing of adm</td>
<td></td>
</tr>
</tbody>
</table>
Note. CODPs = chronic opioid dependent patients; RCT = randomized control trial; IV = independent variable; DV = dependent variable; + = plus; C = control; chronic opioid dependent patients; postop = postoperative; preop = preoperative; intraop = intraoperative; periop = perioperative; ↓ = lower/decreased; ↑ = increased/higher; PCA = patient controlled analgesia; MMT = methadone maintained therapy patients; tx = treatment; WMD = weighted mean difference; CI-confidence interval; hrs = hours; PONV = postoperative nausea and vomiting; VAS = visual analogue scale; ca = cancer; MS = morphine; ME = methadone; MK = methadone and ketamine; NSAIDS = nonsteroidal anti-inflammatory drugs; NMDA = N-methyl-D-Aspartate receptor; CE = continuous epidural; K = ketamine; Quasi Ex = Quasi experimental; OC = opioid consumption; SDM = standard difference in means; ES = effect size; PRISMA = preferred patient reporting items for systematic reviews and meta-analyses; abd. = abdominal; # = number; LAs = local anesthetics; ss = statistically significant.
## APPENDIX D

### TABLE OF EVIDENCE FOR MULTIMODAL ANALGESIA

**Studies Using Multi-Modal Analgesia as a Perioperative Acute Pain Management Modality in Chronic Opioid Dependent Patients Undergoing Surgery Requiring General Anesthesia**

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<tr>
<th>Author(s)</th>
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<th>Measurements</th>
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<tbody>
<tr>
<td>Barreveld et al. (2013)</td>
<td>Decrease postop pain scores with postop K infusion</td>
<td>RCT; IV = K IV 0.2mg/kg/hr + hydromorphone PCA (E); IV placebo (NS) + hydromorphone PCA (C)</td>
<td>59 = 29 (E), 32 (C) randomized; all were CODPs; (excluded-CA pain); general surgery w GA w inhalation agent or TIVA w propofol &amp; remifentanil</td>
<td>NRS = pain preop and postop (worst, least and average) compared to preop; analgesic consumed = hydromorphone PCA total mg; total infusion of K; Nausea scale; pruritis scale; resp. depression = # of episodes in 24 hrs (RR &lt; 8 or SpO2 &lt; 90%); sedation level = modified Ramsey scale; + disturbing dreams; side effects</td>
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<tr>
<td>Mathiesen et al. (2013)</td>
<td>Investigate if standardized</td>
<td>Quasi Ex; no randomization;</td>
<td>44 PIG; 41 POIG; major spine surgery w of life = SF-36 preop, POIG consumed less opioids POD1</td>
<td>SS for POIG ↓ OC POD1 &amp; 2 and early OC POD1 &amp; 2</td>
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</table>

K group had an improved % change in “average pain” (13.5% vs. 15.5% increase in K vs placebo), \( p = .0057 \)

Lack of homogeneity w surgical procedures; variable opioid doses preop in all the pts; lack of control for intraop meds (i.e., remifentanil may cause OIH); duration of K & placebo not standardized

K infusion + hydromorphone PCA postop can reduce “average” pain scores in CODPs.

No change in PCA hydromorphone consumption
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<th>Author(s)</th>
<th>Year</th>
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<tbody>
<tr>
<td>Protocol for postop pain and PONV tx would improve analgesia</td>
<td></td>
<td>IV = standardized tx plan: NSAIDS, Tylenol, gabapentin, K IV 0.5 mg/hr + 0.3 mg/kg/hr intraop, dexamethasone, ondansetron &amp; epidural LA or PCA MS (POIG) DV = OC, side effects &amp; mobilization</td>
<td>multi-level instrumentation; 45 CODPs in the study CODPs w MS &gt; 100mg qd had a different regimen: IV</td>
<td>POD 1-6; pain = NRS @ rest &amp; mvmt qd, POD 1-6; levels of side effects POD 1-6; LOS @ PACU &amp; surg. flr</td>
<td>(p = .024) &amp; 2 (p = .048), earlier ambulation (p = .03), low nausea, sedation &amp; dizziness POD 1-6</td>
<td>Results for CODPs not specified as to differences in OC and QOL</td>
<td>Limitations: Not a RCT; inconsistency in data collection (different data collectors); lack of data from PIG preop; data obtained from POD 1 &amp; 2 w PCA; unable to obtain nausea and dizziness scores for PIG Results for CODPs not specified as to differences in OC and QOL</td>
<td>Were not able to compare pain bt the 2 groups and early ambulation</td>
</tr>
<tr>
<td>Pacreu et al. (2012)</td>
<td>Compare efficacy of K &amp; methadone or methadone alone</td>
<td>RCT; IV = MK and ME DV = pain</td>
<td>20 receiving multi-level lumbar spine surgery with fusion; (E) MK (10) = received pre-incision bolus of 0.5 mg/kg w MK infusion 2.5mcg/kg/min; (C) ME group (10)-bolus of saline w ME infusion; all received GA w 0.2mg/kg/min of remifentanil; prior to closure both received 0.1mg/kg ME, 50 mg</td>
<td>Pain = NRS at rest &amp; movement 24 &amp; 48 hrs postop; sedation postop = Ramsay sedation scale; consumption of ME and K = PCA 24 &amp; 48 hrs</td>
<td>MK group required 70% less opioids post op 24 hrs (p &lt; .001) &amp; 48 hrs (p = .001) Comparable pain postop; MK group PCA attempts 24 hrs postop (p = .043)</td>
<td>In patients with common preop use of opioids (undescribed), post MK PCA ↓ need for postop opioids Small sample size; lacked information regarding type/dose of opioids preop taken; did not perform stats on side effects</td>
<td>↓ OC in MK vs ME</td>
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<td>Author(s)</td>
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<tr>
<td>Subramaniam et al.</td>
<td>2011</td>
<td>Demonstrate efficacy and opioid sparing of low-dose K for CODPs undergoing spine surgery</td>
<td>RCT; IV = K IV (2 mcg/kg/min) (E) vs. saline IV (C) intraop; Both had PCA of hydromorphone &amp; epidural w bupivacaine postop</td>
<td>30 participants-15 (E), 15 (C); lumbar or thoracolumbar laminectomy &amp; fusion; CODPs</td>
<td>Pain = VAS postop x 48 hrs; sedation = (1-5 scale); OC = PCA dose</td>
<td>No improvement in pain scores or OC postop</td>
<td>Did not account for confounding variables: Lacked opioid equivalence among participants; did not disclose other medications that were taken by CODPs (multimodal analgesia); no significant findings</td>
<td>Nothing significant found</td>
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<tr>
<td>Loftus et al.</td>
<td>2010</td>
<td>Effect of intraop K in CODPs</td>
<td>RCT; IV = K 0.5 mg/kg bolus &amp; 10 mcg/kg/min drip (E); saline (C); DV = MS consumption first 24, 48 hrs; pain scores 24 hrs, 48 hrs, 6 wks; PACU discharge time; hospital discharge time</td>
<td>101 CODPs randomized to E (52) or C (50); daily opioid use for 6 wks, CBP, elective lumbar back surgery</td>
<td>Pain = VAS; opiate medication class and dose = MS opioid equivalence</td>
<td>$p &lt; .05$- E required ↓ postop opioids; $p &lt; .05$- intraop K ↓ OC 48 hrs postop (E); no difference in groups with pain intensity first 48 hrs; E required ↓ opiates intraop; immediate PACU pain scores ↓ in both groups</td>
<td>Intraop K ↓ OC in CODPs at 48 hrs postop and 6 wks postop Limitations = adjuvant medications may play a role in these findings</td>
<td>Double blinded; validity of tools not mentioned Useful for citing that K is effective in CODPs intraop E group ↓ OC 24 (p = .029), and 48 hrs (p = .032) postop E group ↓ pain intensity in PACU (p = .03) and @ 6 wks (p = .026)</td>
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<tr>
<td>Urban et al.</td>
<td></td>
<td>Assess the use of Low dose K</td>
<td>RCT</td>
<td>24- (12) C, (12) E</td>
<td>NRS = pain</td>
<td>E = &lt; pain in</td>
<td>Low dose K ↓ Both groups on</td>
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<tr>
<td>Yuan-Yi et al. (1998)</td>
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<td>Examine efficacy of K in mm PCEA for postop pain</td>
<td>RCT; All received PCEA w MS 0.02mg/mL, 0.08% bupivacaine, epi 4 mcg/mL; (E) = also K 0.4 mg/mL</td>
<td>91 participants; 46 (C), 45 (E); 2.5mL/hr + bolus 2.5mLw 4 hr limit of 40 mL started postop</td>
<td>Pain = VAS; recorded at rest &amp; VASC qd x 3 days postop; sedation level; daily PCEA consumption; daily side effects</td>
<td>VASC ↑ in C 3days postop (p &lt; .05); VASR ↑ in C first 2 days postop (p &lt; .05); ↑ opioid use in C first 2 days postop (p &lt; .05)</td>
<td>Adding K in mm PCEA improves analgesia &amp; ↓ OC postop; Limitation: CODPs not identified, unaware of opioid type/dose preop</td>
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<tr>
<td>Lee et al. (2013)</td>
<td></td>
<td>Survey patterns of periop pain mgmt. after spinal surgery; investigate preemptive analgesia &amp; mm on postop pain</td>
<td>Observational study; 17 tertiary hospitals; IV = preemptive analgesia &amp; mm DV = postop pain, quality of life, satisfaction</td>
<td>393 participants; 20% received preemptive analgesia (COX I, ± anticonvulsants) prior to incision; 92% received mm postop pain mgmt.(NSAIDS, COX I, narcotics,</td>
<td>Pain = VAS at preop, DOS, POD1, 2,3,7 &amp;14; Quality of life = EQ-5D day before surgery, POD 14, and 3 months</td>
<td>No preemptive analgesia group required more PCA use vs. preemptive analgesic group (p &lt; .05); EQ-5D improved w preemptive</td>
<td>Limitation: not a RCT; no randomization or control</td>
<td>Only 29 participants (7%) were CODPs-unable to identify if this study was helpful in this group</td>
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**Studies not including ketamine**

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<th>Year</th>
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<th>Results</th>
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<tr>
<td>2008</td>
<td>low dose K as adjunctive therapy in ODPs undergoing spinal surgery</td>
<td>IV = K 2 mcg/kg/hr (E) no K (C) DV = PACU pain and hydromorphone use-measured in PACU, 48 hours at rest and during PT POD 1 and 2</td>
<td>Hydromorphone = PCA SL = 5 point scale Delirium = confusion assessment at PACU and POD1 PT milestones</td>
<td>PACU &amp; POD 1 (p ≤ .05); NSS in hydromorphone use between E and C No difference in PONV, sedation, or PT milestones</td>
<td>postop pain in CODPs after lumbar fusion surgery</td>
<td>Limitation: No ↓ OC in either group</td>
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E = < pain in PACU & POD 1 (p ≤ .05); Useful for citing that intraop K is beneficial postop pain in CODPs |
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<tr>
<td>Rajpal et al. (2010)</td>
<td>Compare spine surgery pts who received IV PCA vs PO multimodal analgesia</td>
<td>Comparison study; Quasi-Ex; no randomization IV = IV PCA, PO multimodal analgesia DV = pain, function, side effects &amp; pt. satisfaction</td>
<td>100 PIG (IV PCA postop) 100 POIG (PO mm-CR-opioid, gabapentin &amp; Tylenol preop and postop w SA opioids PO prn-IV opioids pm for severe pain) all undergoing spine surgeries</td>
<td>Pain = patient survey instrument; Side effects = nausea, vomiting, itching drowsiness; functioning = interference w activity, PT, eating, coughing) = all on 0-10 scale [higher # increased pain/sx]</td>
<td>analgesia group at 2 wks postop (p &lt; .05) ↓ VAS score POD1-14 w preemptive vs non-preemptive (p &lt; .05) ↓ VAS scores w mm group only on POD 14 vs single therapy (p &lt; .05) PCA use ↑ w opioid use preop, those w ↑ VAS preop, non preemptive preop (p &lt; .05)</td>
<td>PO multimodal analgesic regimen ↓ OC for spinal surgery pts SS for less OC and less nausea w mm analgesia vs IV PCA = not a RCT</td>
<td>PO multimodal analgesic regimen ↓ OC for spinal surgery pts Mean “least” pain for mm</td>
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mm group did not have better VAS scores postop; those without preemptive analgesia required ↑ PCA postop
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<td>&amp; accuracy; lack of description of the data collection; a portion of IV PCA group were taking several meds prior to surgery-unsure if these were continued postop? Could affect results</td>
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</table>

Note. CODPs = chronic opioid dependent patients; RCT = randomized control trial; IV = independent variable; DV = dependent variable; + = plus; meds = medications; E = experimental; C = control; PACU = post anesthesia care unit; PT = physical therapy; POD = post operative day; NRS = Numeric Rating Scale; postop = postoperative; preop = preoperative; intraop = intraoperative; periop = perioperative; ↓ = lower/decreased; ↑ = increased/higher; PCA = patient controlled analgesia; MMT = methadone maintained therapy patients; tx = treatment; WMD = weighted mean difference; CI = confidence interval; hrs = hours; PONV = postoperative nausea and vomiting; PCCT = placebo-controlled clinical trial; VAS = visual analogue scale; ca = cancer; MS = morphine; mcg/kg/min = micrograms per kilogram per minute; mm = multi-modal analgesics; PCEA = patient controlled epidural analgesia; ME = methadone; MK = methadone and ketamine; COX I = cyclooxygenase inhibitors; NSAIDS = non steroidal anti-inflammatory drugs; SF-36 = short form health survey; nmvt = movement; PIG = pre-intervention group; POIG = post intervention group; CR = controlled release; SA = short acting; NMDA = N-methyl-D-Aspartate receptor; CE = continuous epidural; K = ketamine; Quasi Ex = Quasi experimental; OC = opioid consumption; LOS = length of stay; SL = sedation level; VASR = visual analogue scale at rest; VASC = visual analogue scale with movement; SS = statistically significant; OIH = opioid induced hyperalgesia; PO = orally; vs = versus; bt = between; w = with; wo = without; TIVA = total intravenous anesthesia; GA = general anesthesia; CBP = chronic back pain; x = for.
## APPENDIX E

### TABLE OF EVIDENCE FOR FENTANYL CHALLENGE

**Fentanyl Challenge and Opioid Dosing in Chronic Opioid Dependent Patients Undergoing Surgery Requiring General Anesthesia**

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<th>Purpose</th>
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<tbody>
<tr>
<td>Determine the amount of intraop fentanyl required for a CODP undergoing open-heart surgery (Davis et al., 2003)</td>
<td>CR</td>
<td>47 yo female taking SR MS 400 mg/day, 2-100mcg/hr TD fentanyl patch, oxycodone 120 mg q 8 hrs Allergic to inhalation agents &amp; benzos</td>
<td>Unresponsiveness; Resp. depression = capnogram and RR; fentanyl Ce = pharmacokinetic simulation software (Stanpump)</td>
<td>Fentanyl Ce was 50-70 times larger than opioid naïve pt.; No postop resp. depression or sedation; pt reported better pain control postop vs. 4 previous open heart surgeries</td>
<td>A helpful tool to estimate intraop opioid requirements</td>
<td>Fentanyl started at 2 mcg/kg/min – after 80 min., ↑ 40 mcg/kg/min after 6 min., pt unresponsive = induced; Ce dose calculated at 25% of that assoc. w unresponsiveness = 33 mcg/kg/hr; postop PCA set to deliver hrly dose at this rate</td>
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<tr>
<td>Estimate postoperative PCA opioid dosing in CODPs based on preop IV fentanyl challenge (Davis et al., 2005)</td>
<td>QEXP/no control group/no randomization; Dose response</td>
<td>19; multilevel posterior spine fusion; PO/TD opioids x 1 month pre surgery</td>
<td>Resp. depression = capnogram and RR; fentanyl Ce = pharmacokinetic simulation software (Stanpump) and PCA demand dose usage</td>
<td>Postop Ce of fentanyl &amp; resp. depression correlated with postop plasma fentanyl levels</td>
<td>Preop fentanyl challenge may be helpful in dosing CODPs postop;</td>
<td>Prior to induction, pts received IV fentanyl 2mcg/kg/min infusion until RR &lt; 5, fentanyl was stopped and GA ensued; intraop fentanyl rate (per Ce) 30% associated with resp. depression; postop PCA basal infusion 50% of total hourly requirement; basal infusion ↑ or ↓ per pts. demand dose use</td>
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Useful as option for dosing surgical CODPs
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<td>PaO2 after stable PCA infusion x 24 hrs and no adjustments for 8 hrs</td>
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*Note.* CODPs = chronic opioid dependent patients; RCT = randomized control trial; IV = independent variable; DV = dependent variable; + = plus; meds = medications; E = experimental; C = control; PACU = post anesthesia care unit; PT = physical therapy; POD = post operative day; postop = postoperative; preop = preoperative; intraop = intraoperative; periop = perioperative; ↓ = lower/decreased; ↑ = increased/higher; PCA = patient controlled analgesia; MMT = methadone maintained therapy patients; tx = treatment; Ce = effect site concentration; SR = sustained release; MS = morphine; hr = hour; PO = oral; TD = transdermal; QEXP = quasi-experimental; benzos = benzodiazepines; pts = patients; RR = respiratory rate; y.o. = years of age; mg/day = milligrams per day; mcg/hr = micrograms per hour; mg = milligrams; hrs = hours; mcg/kg/min = micrograms per kilogram per minute; GA = general anesthesia; min = minutes; CR = case report; with = with; x = for.
### APPENDIX F

#### TABLE OF EVIDENCE OF META ANALYSES FOR INTRAVENOUS LIDOCAINE

**Meta Analyses of Lidocaine as a Perioperative Acute Pain Management Modality in Chronic Opioid Dependent Patients Undergoing Surgery Requiring General Anesthesia**

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<tr>
<td>Evaluate efficacy of systemic lido in postop pain after abd. surgery (Sun et al., 2012)</td>
<td>Meta-analysis; PRISMA guidelines</td>
<td>21 RCTs (N = 1108); n = 584 that received systemic lido; Lido initiated preop in 17 studies &amp; 4 postop; Lido bolus 100 mg or 1.5-2 mg/kg/hr w infusion at 1.5-3 mg/min until EOS or 1.4, or 24 hrs postop</td>
<td>OC = total mg; pain = VAS @ 6, 24, &amp; 72 hrs; LOS; opioid related side effects; plasma cytokine levels @ 24 hrs postop</td>
<td>Postop pain @ 6 hrs, at rest in 11 RCTs &amp; during activity in 7 RCTs = lower in lido group = WMD of pain at rest was -8.07mm ([95% CI, -14.69,-1.49]; $I^2 = 90.6%$), &amp; -10.56 mm[95% CI-16.89,-4.23]; $I^2 = 82%$ during activity</td>
<td>Lack of homogeneity among surgical procedures (open vs. lap and type)</td>
<td>Unsure if CODPs are included</td>
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<td>Pain 24 hrs postop 13 RCTs at rest &amp; 9 w activity = SS ↓ in pain @ rest in lido group (WMD -4.41mm [95% CI, -7.70,-1.13]; $I^2 = 67.8%$) &amp; during activity (WMD-4.04 mm [95% CI,-8.00,-0.09]; $I^2 = 5.6%$)</td>
<td>Lido may be useful in ↓ OC and postop pain in abd. surgeries</td>
<td>Did not disclose of CODPs were included in this study = assume that CODPs are included</td>
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<td>Pain @ 72 hrs postop NS</td>
<td>Lido may be useful in ↓ OC and postop pain in abd. surgeries</td>
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<td>OC 14 RCTs analyzed = ↓ OC in lido group vs</td>
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<tr>
<td>Evaluate efficacy &amp; safety of IV lido during GA in all surgical types (Vigneault et al., 2011)</td>
<td>Meta analysis; PRISMA</td>
<td>29 RCTS ($n = 1754$) that used IV lido and a placebo/comparator during GA for any surgery</td>
<td>Pain scores = VAS or equivalent @ 6, 12, 24, 48, and 72 hrs; Opioid use = MS equivalence used; LOS = PACU &amp; hospital; mortality; adverse effects; time to first flatus</td>
<td>placebo (WMD-7.04mg [95% CI -10.40, -3.68]; $I^2 = 46.1$%)</td>
<td>LOS = NS; Side effects = NS</td>
<td>Plasma cytokine levels = only 3 RCTs = level of IL-8 was lower in lido group vs placebo; IL-1ra was not different</td>
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<td>Pain (19 RCTs) = postop pain @ rest @ 6 hrs SS (9 studies, $n = 579$), WMD -8.70, [95% CI -16.19, -1.21]; postop pain @ 12 hrs SS (6 studies, $n = 389$, WMD -6.52), [95% CI -12.2, -0.91]</td>
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<td>IV lido ↓ pain scores @ 6 &amp; 12 hours @ rest; @ 6, 12, &amp; 24 hrs postop w cough in mainly abd.surgeries, ↓ pain w movement in non abd. surgeries; ↓ OC</td>
<td>Unable to determine if it is efficacious in CODPs</td>
<td>Does not identify how many studies included CODPs</td>
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<td>Assess efficacy of IV lido on abd. surgery recovery (Marret et al., 2008)</td>
<td>Meta analysis; QUORUM</td>
<td>8 RCTs (*6 RCTs excluded CODPs); (7 RCTs lido bolus 1.5 mg/kg prior to incision w infusion intraop and postop-1 RCT lido infusion started 30 min prior to incision); All RCTs placebo groups received IV saline</td>
<td>Pain = VAS 24 &amp; 48 hrs postop; OC; incidence of opioid use; time to first flatus; LOS</td>
<td>Postop ileus ↓ w IV lido (WMD -8.36 [95% CI -13.24,-3.47] hrs; p &lt; 0.001)</td>
<td>Postop pain included 6 RCTs (n = 250) *not disclosed if CODPs were in the sample</td>
<td>IV lido ↓ postop ileus, LOS, postop pain @ 24 hrs, &amp; PONV in abd. surgeries--unable to determine if it is efficacious in CODPs</td>
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<td>LOS ↓ w IV lido (WMD -0.84 [95% CI, -1.38, -0.31] days; p = .002)</td>
<td>Did not disclose which RCTs included CODPs and sample sizes</td>
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<td>Postop pain @ 24 hrs ↓ w IV lido (WMD -5.93 [95% CI, -9.63,-2.23]; p = .002)</td>
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<td>PONV incidence 32% lido group vs 52% placebo (odds ratio 0.39)</td>
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<td>[95% CI, 0.20, 0.76]; ( p = .006 )</td>
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**Note.** CODPs = chronic opioid dependent patients; RCT = randomized control trial; IV = independent variable; DV = dependent variable; + = plus; E = experimental; C = control; PACU = post anesthesia care unit; POD = post operative day; postop = postoperative; preop = preoperative; intraop = intraoperative; \( \downarrow \) = lower/decreased; \( \uparrow \) = increased/higher; PCA = patient controlled analgesia; VAS = visual analogue scale; LOS = length of stay; EOS = end of surgery; PRISMA = preferred reporting items for systematic reviews and meta analysis; SS = statistically significant; WMD = weighted mean difference; IL-8 = interleukin 8; IL-1ra = interleukin 1ra; lap = laparoscopy; IV = intravenous; lido = lidocaine; GA = general anesthesia; QUORUM = quality of reporting of meta-analyses; OC = opioid consumption; MS = morphine; mg = milligrams; mg/kg/hr = milligrams per kilogram per hour; mg/min = milligrams per minute; hrs = hours; abd. = abdominal; CI = confidence interval; NS = nothing significant; PONV = postoperative nausea and vomiting; w = with; vs = versus; mg/kg = milligrams per kilogram.
## APPENDIX G

### TABLE OF EVIDENCE FOR INTRAVENOUS LIDOCAINE

*Randomized Controlled Trials of Lidocaine as a Perioperative Acute Pain Management Modality in Chronic Opioid Dependent Patients Undergoing Surgery Requiring General Anesthesia*

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<tr>
<td>Hypothesize that periop IV lido ↓ postop pain scores and OC (Farag et al., 2013)</td>
<td>RCT; IV = IV lido DV = OC and pain scores Pts undergoing multilevel spine surgery w or without instrumentation</td>
<td>C (58), E (57); E prior to induction received IV lido 2mg/kg/hr infusion until DC’d from PACU or 8 hrs; C received equal volume of NS</td>
<td>Pain = VRS @ 30min intervals in PACU. q 4-6 hrs thereafter OC-MS equivalents during first 48 hrs postop</td>
<td>IV lido superior on subjective pain was found versus placebo ($p &lt; .001$) [95% CI, adjusted mean of 4.4, 4.2-4.7 and 5.3, 5.0-5.5]</td>
<td>IV lido improves postop pain in spine surgery pts CODPs included (19) C, (9) E; Limitations: varying degrees of invasiveness of spine surgery; no subgroup analysis of CODPs</td>
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<tr>
<td>Assess the efficacy of IV lido intraop. (Kim et al., 2013)</td>
<td>RCT; IV = IV lido DV = pain scores Early gastric cancer pts undergoing lap assist distal gastrectomy surgery</td>
<td>C (17), E (17); E intraop received Lido bolus 1.5 mg/kg w lido infusion @ 2mg/kg/hr; C received same amt of NS; IV PCA of fentanyl 20 mcg/kg @ 1ml/hr w 1ml/dose lockout 15 min</td>
<td>Pain = VAS @ 2, 4, 8, 12, 24 and 48 hrs postop; BHC @ 2, 2-4, 4-8, 8-12, 12-24, &amp; 24-48 hrs postop.</td>
<td>VAS scores @ 2, 4, 8, 12, &amp; 24 hrs ↓ in E group ($p &lt; .05$) as compared to C; BHC &amp; fentanyl consumption ↓ in E group ($p &lt; .05$) as compared to C</td>
<td>IV lido ↓ fentanyl consumption &amp; postop pain in lap assisted distal gastrectomy Limitations: does not disclose if CODPs included in study; small sample size; did not disclose when IV lido DC’d (assume only infused intraop)</td>
<td>Assume that CODPs are included in the study IV lido ↓ postop fentanyl consumption and pain in lap assisted distal gastrectomy</td>
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</tbody>
</table>

*Note.* CODPs = chronic opioid dependent patients; RCT = randomized control trial; IV-independent variable; DV = dependent variable; + = plus; meds = medications; E = experimental; C = control; PACU = post anesthesia care unit; PT = physical therapy; POD = post operative day; postop = postoperative; preop = preoperative; intraop = intraoperative; periop = perioperative; ↓ = lower/decreased; ↑ = increased/higher; PCA = patient controlled analgesia; MMT = methadone maintained therapy patients; BHC = button hit counts; lap = laparoscopic; lido = lidocaine; IV = intravenous; mg/kg/hr = milligrams per kilogram per hour; mg/kg = milligrams per kilogram; DC’d = discontinued; hrs = hours; NS = normal saline; MS = morphine; OC = opioid consumption; VAS = visual
analogue scale; VRS = verbal rating scale; mcg/kg = micrograms per kilogram; pts = patients; w = with; ml/hr = milliliters per hour; ml = milliliters; CI = confidence interval.