UCSF
UC San Francisco Electronic Theses and Dissertations

Title

The Association of Demographics, Opioid Use History, Mental Health History, and/or Surgery Type with Administration of Low-dose Intravenous Ketamine in the Post-Anesthesia Care Unit

Permalink

https://escholarship.org/uc/item/8763m9wp

Author

Thomas, Ashley

Publication Date

2024

Peer reviewed|Thesis/dissertation

eScholarship.org Powered by the California Digital Library
University of California

The Association of Demographics, Opioid Use History, Mental Health History, and/or Surgery Type with Administration of Low-dose Intravenous Ketamine in the Post-Anesthesia Care Unit

by

Ashley Thomas

THESIS

Submitted in partial satisfaction of the requirements for degree of

MASTER OF SCIENCE

in

Nursing

in the

GRADUATE DIVISION

of the

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

Approved:

DocuSigned by:
Michele Pelter
190CFABB136B4BD...

Michele Pelter

Chair

DocuSigned by:
Maria Yefimova
D...

Maria Yefimova

DocuSigned by:
Heather Leutwyler
012039073579437...

Heather Leutwyler

Committee Members

Copyright 2024

by

Ashley Thomas

Acknowledgments

I would like to thank my thesis advisor, Dr. Pelter, for her invaluable guidance and support throughout this process. Your expertise, kindness, patience, and leadership are truly appreciated and respected. Dr. Bazinski, thank you for your steadfast support and mentorship during this process and beyond. Your expertise in pain management and unwavering support for the Clinical Nurse Specialist (CNS) profession are truly inspiring and played a key part in leading me to the path of CNS. I feel privileged to have the opportunity to learn and collaborate with you both as a renowned nurse scientist and professional and personal mentor.

Thank you to all interdisciplinary collaborators: Korana Avdagic, Ela Borczynski, Benjamin Michaels, Dr. Thomas Hoffmann, Dr. Maria Yefimova, Dr. Heather Leutwyler, and Dr. Hildy Schell-Chaple.

To UCSF School of Nursing and UCSF Health for providing the opportunity to participate in the Clinical Nurse Research grant program and funding this study.

To my partner, thank you for your continued encouragement and support in all my professional aspirations.

The Association of Demographics, Opioid Use History, Mental Health History, and/or Surgery Type with Administration of Low-dose Intravenous Ketamine in the Post-Anesthesia Care Unit

Ashley Thomas

Abstract

Introduction: Patients on chronic opioid therapy (COT) who are admitted for a planned surgical procedure may experience inadequately controlled pain in the post-anesthesia care unit (PACU) due to drug tolerance. This is disruptive for not only patients but PACU nurses and can lead to increased utilization of hospital resources and extend PACU and hospital length of stay. Pain management may be optimized in this group using low-dose intravenous (IV) ketamine. However, in a pilot study, we found that administration of this medication occurred 114 minutes (range 14 minutes to 394 minutes) after admission to the PACU, with resultant sub-optimal pain management and delays in PACU throughput. We hypothesize that identifying patients in the preoperative phase who may benefit from this therapy could reduce administration delays and improve pain management. However, specific patient-level variables that may be useful to screen for are largely unknown. **Purpose**: Examine demographics, opioid use history, mental health diagnosis, and/or surgical service type associated with the administration of low-dose IV ketamine in the PACU. **Methods**: Retrospective study in 6,419 consecutive adult patients (≥18 years) presenting for a scheduled surgical procedure between Jan 1, 2020, and Dec 31, 2021. The outcome variable was the administration of a low-dose IV ketamine infusion in the PACU. Hypothesized patient predictors were obtained from the electronic health record. A stepwise regression model was used to identify statistically significant variables. **Results:** In 6,419 consecutive patients, 90 (1.4%) received low-dose IV ketamine in the PACU. Significant variables in the final stepwise model included: age of 55-71 years (p=0.029); history of opioid or substance use disorder (p<0.001); outpatient opioid prescription (p=0.025); outpatient methadone prescription (p=0.049); and morphine milligram equivalency (MME) ≥90/day

(p<0.001). **Conclusion:** Two variables had the highest odds ratio associated with low-dose IV ketamine in the PACU. Patients with an MME ≥90/day were 13.26 times more likely to have received low-dose IV ketamine in the PACU and those with SUD/OUD were 4.02 times more likely to have received low-dose IV ketamine in the PACU. **Implications for Practice and Future Research:** Nurses should consider evaluating patients in the preoperative phase of care for MME ≥90/day and those with SUD/OUD, as these appear to be important predictors of low-dose IV ketamine in the PACU. However, a larger patient cohort of patients who received low-dose IV ketamine in the PACU is needed to further develop and test a preoperative screening tool.

Table of Contents

Introduction 1

Purpose 5

Methods 6

Study Design and Sample 6

Setting 6

Variables of Interest 6

Statistical Analysis 7

Results 7

Demographics 7

Surgical Type 8

Mental Health History (ICD-10 Codes) 8

Opioid Use History (EHR derived) 9

Stepwise Model 9

Discussion 10

Surgical Type 10

Mental Health History 11

Opioid Use History 12

Limitations 13

Conclusions 13

List of Tables

Table 1. Definitions of variables examined. 14

Table 2. Demographics and surgical service type 15

Table 3. Mental health diagnoses 16

Table 4. Opioid use history 17

Table 5. Stepwise Model 18

Introduction

Acute postoperative pain is common, with 80% of surgical patients experiencing any pain and 75% reporting moderate, severe, or extreme pain (Chou et al., 2016; Gan, 2017; Gan et al., 2014). Inadequately controlled postoperative pain is associated with an increased risk of morbidity (e.g., myocardial infarction, decreased vital capacity, pulmonary infection, ileus, vomiting, urinary retention, coagulopathy), impaired level of functioning and quality of life, prolonged recovery, and impaired wound healing (Gan, 2017). Additionally, uncontrolled pain can lead to the development of chronic pain, prolonged opioid use, negative psychological effects, and increased costs of care (Gan, 2017). A national survey conducted in the United States (U.S.) by the National Center for Health Statistics in 2019, found that among adults living with chronic pain, 22.1% had used a prescription opioid within the past 3 months, which was higher among women and those aged 45 to 64 (Dahlhamer, 2021). Interestingly, the presence of pain preoperatively and use of preoperative analgesia or opioids, is negatively associated with poor postoperative pain control (Gan et al., 2014; Yang et al., 2019).

Opioid medications for postoperative pain management are commonly prescribed in the U.S. and at higher rates compared to non-U.S. countries (El Moheb et al., 2020; Kaafarani et al., 2020; Ladha et al., 2019). However, opioid medications pose significant risks to patients, such as respiratory depression, somnolence, opioid tolerance (OT), opioid dependence (OD), central sensitization, opioid-induced hyperalgesia, overdose, and death (Carr, 2023; Dowell et al., 2022; Gan, 2017). Also reported are several associated side effects (i.e. constipation, urinary retention, nausea, vomiting, dizziness, pruritus, confusion, inability to operate a vehicle) that can negatively impact quality of life. Importantly, patients taking opioids *preoperatively* are more likely to have poor surgical outcomes, increased morbidity, longer length of hospital stay, higher hospital costs, and increased readmission rates (Cron et al., 2017; Jain et al., 2018; Waljee et al., 2017). Opioid-induced adverse events, such as advancing sedation and

respiratory depression, can lead to deadly and costly consequences for both patients and hospitals (Jungquist et al., 2020). According to the Centers for Disease Control and Prevention (CDC), of the overdose deaths in 2021, opioids were involved in 80,411 cases, which is equivalent to 75.4% of all drug overdose deaths (CDC, 2023). The economic burden of opioid use disorder (OUD) and fatal overdose (overall) in 2017 was $1.02 trillion (Florence et al., 2021).

The CDC defines OT as, “when a person using opioids begins to experience a reduced response to medication, requiring more opioids to experience the same effect” (CDC, 2021). The U.S. Food and Drug Administration (FDA) further defines OT as “those taking, for one week or longer, at least 60 mg of morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg of oral oxycodone per day, 8 mg of oral hydromorphone per day, 25 mg oral oxymorphone per day, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid” (FDA, 2015). Chronic opioid therapy (COT), is now a commonly used term and is most frequently defined in the literature as prescribed opioids for >90 days (Shen et al., 2021). OD “occurs when the body adjusts its normal functioning around regular opioid use. Unpleasant symptoms occur when medications are stopped” (CDC, 2021). OUD “occurs when attempts to cut down or control use are unsuccessful or when use results in social problems and a failure to fulfill obligations at work, school, and home” (CDC, 2021).

Patients on COT presenting for surgery come with unique challenges and increase the complexity of postoperative pain management due to potential OT, central sensitization, and opioid-induced hyperalgesia (Carr, 2023). Patients who are OT or on COT are often not identified preoperatively or may fail to report accurate opioid use history at their preoperative visit, which can result in uncontrolled or inadequately controlled pain in the post-anesthesia care unit (PACU). Uncontrolled pain in the PACU is a concern for patients but also creates workflow interruptions and adds complexity to care delivery among nurses and providers. For example, COT patients require more PACU resources due to high pain medication requirements and often

1-on-1 care, which can result in delayed pain management and prolonged PACU recovery time. This causes a cascading effect whereby the primary nurse cannot care for a second patient, and the PACU bed is not efficiently turned over for future operating room (OR) patients, ultimately affecting all perioperative patients and throughput.

A multimodal, patient-centered, perioperative analgesic approach (i.e., the use of multiple pharmacological classes with different underlying mechanisms) is recommended for surgical patients to achieve better pain control, reduce the escalation of one single analgesic agent, and promote opioid stewardship (Chou et al., 2016; Edwards et al., 2019; Goldberg et al., 2017; Hyland et al., 2021; Schwenk & Mariano, 2018; Schwenk et al., 2018). Additionally, it is recommended clinicians assess for specific patient variables (i.e., demographics, medical and psychiatric comorbidities, medications, pain history, substance use history, and previous responses to postoperative pain regimens) during the preadmission and preoperative phase to assess for potential predictors of acute postoperative pain, and to optimize multimodal analgesia and recovery (Chou et al., 2016; Edwards et al., 2019; Hyland et al., 2021; Yang et al., 2019).

Ketamine, a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist derived from phencyclidine, not an opioid, is becoming more commonly used as a component of postoperative multimodal analgesia regimens. Ketamine modulates pain at the dorsal horn of the spinal cord by blocking the NMDA receptor sites and preventing glutamate activation and neuronal excitation associated with central sensitization (Gorlin et al., 2016). Ketamine is particularly useful in patients who are OT or develop opioid-induced hyperalgesia because central sensitization is implicated in both instances (Carr, 2023). The safety and efficacy of low-dose IV ketamine for acute postoperative pain management concerning reduced postoperative pain scores and opioid consumption have been well established, especially among painful surgeries with patients presenting with chronic pain and on COT (Boenigk et al., 2019; Jouguelet-Lacoste et al., 2015; Murphy et al., 2021; Pendi et al., 2018; Zhou et al., 2022).

Additionally, recently published consensus guidelines from the American Society of Regional Anesthesia (ASRG), the American Academy of Pain Medicine (AAPM), and the American Society of Anesthesiologists (ASA) recommend the use of subanesthetic, low-dose IV ketamine as an analgesic adjunct to opioids for the management of acute pain. Specifically for those expected to have severe postoperative pain, are OT or OD, and/or are at increased risk of respiratory depression associated with opioids (Schwenk et al., 2018). Ketamine is also a useful adjunct for painful surgical procedures where regional anesthesia techniques are not feasible (Goldberg et al., 2017).

While these guidelines and evidence support the use of postoperative ketamine for patients presenting for surgery using COT or known OT, this practice remains underutilized due to a lack of protocols and sufficient evidence surrounding specific patient characteristics aside from surgery type and opioid use history. In a pilot study (unpublished) conducted at our hospital among 43 PACU patients who had received a postoperative, low-dose IV ketamine infusion, 41 (95%) were identified as having chronic pain documented in an acute pain service provider note (Thomas et al., 2022). We examined the time from patient arrival in the PACU to administration of ketamine and found that the median time the order was placed was 67 minutes (range -23 minutes to 351 minutes). Furthermore, the median time from the ketamine order to administration by the nurse was 47 minutes (range 15 minutes to 257 minutes). Thus, the median time from arrival in the PACU to administration of the ketamine infusion was 114 minutes (range 14 minutes to 394 minutes). Interestingly, 29 (67%) received intraoperative ketamine, but it was discontinued before PACU arrival. We concluded that the delay in administering low-dose IV ketamine was associated with our hospital's process. Furthermore, we hypothesize that identifying specific patient characteristics associated with administering postoperative, low-dose IV ketamine in the PACU may assist in developing a preoperative screening tool to identify patients who may benefit from postoperative ketamine, thus improving postoperative pain management and throughput.

There are published studies regarding patient characteristics associated with COT. Jain et al. (2018) conducted a retrospective analysis of patient characteristics associated with those undergoing posterior lumbar fusion on preoperative COT. They found that a diagnosis of anxiety, depression, inflammatory arthritis, tobacco use disorder, and drug abuse/dependence were associated with COT (Jain et al., 2018). In a separate study, prescription opioid use among adult patients with chronic pain varied by age, sex, education level, employment status, poverty status, and health insurance coverage (Dahlhamer, 2021). The American Society for Enhanced Recovery and Perioperative Quality Initiative (ASERP) released a joint consensus statement recommending a novel classification scheme (opioid-naïve, exposed, and tolerant+ [O-NET+]) for clinicians to employ during the preoperative phase of care to risk stratify patients according to their preoperative opioid exposure (naïve, exposed, tolerant) while taking into account additional modifiable risk factors (psychiatric history, substance use disorder, surgery type) that have been shown to impact postoperative pain as well as opioid use. This approach is hypothesized to allow clinicians the opportunity to employ a risk-based management plan well before the day of surgery to optimize postoperative pain and reduce opioid-related adverse events (ORAEs) (Edwards et al., 2019). Based on the above studies and consensus guidelines, we examined patient variables to determine if these were associated with the administration of ketamine in the PACU.

Purpose

The purpose of this study was to examine if demographics, opioid use history, mental health diagnosis, and/or surgery type were associated with the administration of low-dose IV ketamine in the PACU among a cohort of 6,419 consecutive patients presenting for a scheduled surgical procedure.

Methods

Study Design and Sample

This was a retrospective, observational study conducted at a 600-bed academic medical center between 2020 and 2021. The institutional review board approved the study (IRB# 21-35195) with a waiver of signed informed consent due to the observational and retrospective nature of the study. We included consecutive adults ≥18 years of age who were admitted for a scheduled surgical procedure and were evaluated in the preoperative clinic before surgery. We excluded patients not admitted to the PACU postoperatively (e.g., directly admitted to intensive care) or discharged home the same day of surgery.

Setting

The perioperative department comprises 28 operating rooms (OR), 1 procedural suite, 15 preoperative (PREOP) beds, and 22 PACU beds. The PACU receives patients undergoing surgery within an OR and those with procedures conducted in non-operating room areas (e.g., radiology, endoscopy, catheterization laboratory, electrophysiology lab). On average, the PACU admits 60 adult and adolescent patients daily who undergo inpatient and outpatient surgical procedures. Surgery types include general, vascular, cardiac, cardiothoracic, orthopedic, transplant, neurological, plastic, ophthalmology, otolaryngology head and neck, oral and maxillofacial, genitourinary, gastroenterology, surgical oncology, bariatric, and radiology. The PACU staff comprises 73 registered nurses (RNs) and 20 patient care assistants/technicians. The minimum required recovery time for patients receiving general anesthesia is one hour, and patients must meet certain discharge criteria, including reported tolerable pain level, before transfer to an inpatient unit or discharge home.

Variables of Interest

Data were obtained from the electronic health record (EHR). International Classification of Diseases, Tenth Revision (ICD-10) codes were used to identify the variables of interest.

Demographics, psychosocial, opioid use history, and surgical service type were also obtained from the EHR. **Table 1** shows the variables extracted from the EHR and their definitions. The variables selected were based on prior studies that show preoperative predictors associated with poorly controlled postoperative pain, common variables found among adult patients on COT, expert consensus guidelines and studies stating the efficacy and safety of low-dose IV ketamine for patients undergoing painful surgeries, and a novel classification scheme to asses for preoperative opioid exposure and modifiable risk factors (Boenigk et al., 2019; Dahlhamer, 2021; Edwards et al., 2019; Jain et al., 2018; Jouguelet-Lacoste et al., 2015; Murphy et al., 2021; Pendi et al., 2018; Schwenk et al., 2018; Yang et al., 2019; Zhou et al., 2022).

Statistical Analysis

Statistical analyses were conducted under the guidance of a statistician. Descriptive statistics, including frequencies and means (standard deviation), were used to describe the sample and variables of interest. The administration of low-dose IV ketamine in the PACU was the dependent variable. Univariate analyses were used to identify variables to include in forward stepwise regression models. A p-value <0.05 was used to determine variables to include in the stepwise models. All statistical analyses were conducted using R (v4.3.2; R Core Team 2023).

Results

Demographics

A total of 6,419 consecutive patients were included, and 90 (1.4%) received low-dose IV ketamine in the PACU (**Table 2**). In the overall sample, age categories, were similar by group (yes ketamine versus no ketamine). Of the total, 52.6% were female (3,379) and race reflected the varied racial makeup (40.9% non-white) of our hospital's geographic location. Twenty-six (0.04%) had housing insecurity.

In comparing the groups (yes versus no ketamine), a higher proportion of those aged 55 to 63 (28.9% versus 18.4%) and those aged 63 to 71 (27.8% versus 20.9%) received ketamine

(p=0.0014). Those aged 71 to >90 had the lowest rate (7.8% yes versus 21.6% no). There were no differences by sex or housing insecurity, although the latter group was a small sample. With regards to race, White patients had the highest proportion of ketamine use (73.3% yes versus 58.9% no), and Asian patients had the lowest rate (3.3% yes versus 11% no). Latinx patients had a slightly higher rate (8.9% yes versus 16.7% no). Black/African American, Multi-Race and Other Race had similar proportions.

Surgical Type

There were seven different surgical service types, with neurological (1,983; 30.9%) and orthopedic (1,414; 22%) surgery being the most common **(Table 2).** A total of 9.7% (n=623) had an "other" surgical service type. Neurological surgeries represented the highest proportion of all the surgical service types; 37.8% received ketamine, and 30.8% did not (p=0.00068). The orthopedic surgical service type was the second most common (22%), and a higher proportion of this group received ketamine (34.4%) as compared to no ketamine (21.9%). A total of 8.2% of the sample had a transplant surgery type (n=529), but only one patient had ketamine (1.1%). Similar proportions (ketamine versus no ketamine) were seen for the other surgical service types.

Mental Health History (ICD-10 Codes)

Mental health history variables by ketamine group (yes versus no) are shown in **Table 3**. Patients with a mental health diagnosis were more likely to receive low-dose IV ketamine (32.2% ketamine versus 17.1% no ketamine; p = <0.00061). However, among the ketamine group, a higher proportion of those *without* a documented mental health diagnosis received ketamine (67.8%; 61 of 90). Patients with psychoactive substance use disorder were more likely to receive low-dose IV ketamine (23.3% ketamine versus 5.4% no ketamine; p <0.00001). However, among the ketamine group, a higher proportion of those *without* a documented psychoactive substance use disorder received ketamine (76.7%; 69 of 90). Lastly, patients with

a mood (affective) disorder were more likely to receive low-dose IV ketamine (21.1% yes versus 8.5% no; p = <0.00019). However, similar to the above, among the ketamine group, a higher proportion of those *without* a documented mood (affective) disorder received ketamine (78.9%; 71 of 90).

Opioid Use History (EHR derived)

Opioid use history, except for documented outpatient buprenorphine prescription, by group is shown in **Table 4**. Patients with substance/opioid use disorder (SUD/OUD), documented MME ≥90/day, an outpatient opioid prescription, and an outpatient methadone prescription were more likely to receive low-dose IV ketamine. Of the overall sample, only 16.3% of patients had documented MME ≥90/day. Seventy-eight percent of the patients who received ketamine had documented MME ≥90/day versus 13.1% who did not receive IV ketamine (p<0.0001). Of the overall sample, 1.7% had documented SUD/OUD. When comparing the groups, a higher proportion of those who received ketamine had a documented SUD/OUD (15.6%) compared to those who did not receive ketamine (1.5%) (p<0.0001). Of the overall sample, 20.7% had a documented outpatient opioid prescription. Sixty-seven percent of the patients who received ketamine had a documented outpatient opioid prescription versus 20% who did not receive ketamine (p<0.0001). Interestingly, a higher proportion of those *without* a documented SUD/OUD (84.4%) or an outpatient prescription for methadone (92.2%) received low-dose IV ketamine.

Stepwise Model

In the initial stepwise model, age, race/ethnicity, surgical service, mental health history, substance/opioid use disorder, MME ≥90/day, outpatient opioid prescription, and outpatient methadone prescription (significant in univariate analysis) were included. Variables that remained in the final model are shown in **Table 5** and include MME ≥90/day, SUD/OUD, outpatient methadone prescription, and outpatient opioid prescription and age. Patients with

MME ≥90/day were 13.26 times more likely to receive low-dose IV ketamine in the PACU, and those with SUD/OUD were 4.02 times more likely to receive low-dose IV ketamine in the PACU.

Discussion

Our study examined associations of demographics, opioid use history, history of mental health diagnoses, and/or surgical service type associated with the administration of low-dose IV ketamine in the PACU, which adds to our understanding of potential predictors present before scheduled surgery. Patients who were 55 to 63, or 63 to 71, were White and had neurological or orthopedic surgery types had the highest rate of low-dose IV ketamine in the PACU. Dahlhamer et. al, (2021) showed similar proportions of adults with chronic pain on COT among these age groups (Dahlhamer, 2021). Two variables had the highest odds ratio associated with low-dose IV ketamine in the PACU. Patients with an MME ≥90/day were 13.26 times more likely to receive low-dose IV ketamine in the PACU, and those with SUD/OUD were 4.02 times more likely to receive low-dose IV ketamine in the PACU. Of note, while the above variables were more frequent in ketamine versus non-ketamine patients, when examining the ketamine-only group (n=90), often a higher proportion of patients *without* a mental health diagnosis (ICD-10 code), history of SUD/OUD, or outpatient prescription for methadone or buprenorphine received ketamine. This suggests that many PACU patients will not have a documented history of the variables we tested but will go on to receive low-dose IV ketamine in the PACU; hence, further evaluation of variables associated with low-dose IV ketamine in the PACU is needed.

Surgical Type

The most common surgical service type among patients who received low-dose IV ketamine in the PACU was neurological and orthopedic surgery. Most notably, 63% (57/90) of the ketamine group underwent surgeries focused on the spine. This may be because spinal surgeries are known to be more painful, and regional or neuraxial analgesia is often not feasible in these cases. Our findings support current evidence, suggesting that ketamine is a useful

adjunctive analgesic agent in patients undergoing painful surgeries, such as spinal surgeries (Murphy et al., 2021; Pendi et al., 2018).

Mental Health History

Of the six mental health diagnoses we examined, patients with mental and behavioral disorders due to psychoactive substance use, mood (affective) disorders, or any of the six diagnoses categories we examined (mental health diagnosis) were more likely to receive ketamine in the PACU. Our findings support the ASERP consensus statement that modifiable risk factors (psychiatric history, substance use disorder, surgery type) have been shown to impact postoperative pain as well as opioid use (Edwards et al., 2019). However, in our study, among the ketamine group (n=9), 67.8% did not have a documented mental health diagnosis, while 32.2% had this diagnosis. This may be due to this variable not being documented in the EHR by a provider, or the patient may not have reported this. However, this may also suggest that patients who receive ketamine do not have a mental health condition, which was found in the final stepwise model.

The proportion of patients who received ketamine with a documented mental and behavioral disorder due to psychoactive substance use (ICD-10 F10-19) (23.3%) was slightly higher yet similar in proportion to those with documented SUD/OUD history (15.6%). SUD/OUD-specific ICD-10 codes are included in this broad ICD-10 category, so this appears useful. However, 76.7% of patients who received ketamine did not have a documented ICD-10 code for this category, whereas 23.3% of the ketamine group had a documented diagnosis within this category. This may be due to this diagnosis not being documented, or perhaps some patients were maintained on their outpatient medications for OUD (methadone or buprenorphine) in the perioperative period; thus, their postoperative pain was well managed. They may also have undergone surgeries that were not as painful or where regional anesthesia was utilized. Furthermore, because psychosis is a contraindication for ketamine administration, it is perhaps

not surprising that patients in our study with a history of a psychotic disorder (0.3%) did not receive ketamine (Schwenk et al., 2018).

Opioid Use History

In our study, 77.8% of patients who received ketamine had documentation of taking 90 or more MME per day, while 22.2% of this group did not. This may suggest that patients who received a ketamine infusion had a lower daily MME, and a future analysis may be warranted with a lower MME cutoff point, such as MME of 60 or more. Our findings support the ASERP consensus statement that assessing patients for opioid-naïve, exposed, and tolerant+ [O-NET+]) during the preoperative phase of care may be a reasonable strategy to risk stratify patients according to their preoperative opioid exposure. Of note, 13.1% of those who did not receive ketamine had documentation of taking 90 or more MME/day, which may suggest that these patients may have been taking long-acting methadone or buprenorphine; received a different type of analgesic regimen, such as regional anesthesia; had a contraindication for receiving ketamine; or were not prescribed ketamine but may have benefited from this approach.

Among the patients in our study with a documented opioid prescription, 66.7% of those who received ketamine had this documented in their medication record, while 33.3% who received ketamine did not. It is possible that the 33.3% of patients who did not have documentation of taking an opioid prescription before scheduled surgery were either using illicit opioids, their medication record was inaccurate, or they received ketamine for other reasons. Of note, 20% of patients who did not receive ketamine had documentation of an outpatient opioid prescription. This may suggest that this group may have potentially benefited from ketamine, or they may not have developed OT because of a lower outpatient MME, the duration of opioid therapy was not long enough to develop OT, or they underwent a surgical procedure where regional anesthesia was used to manage their postoperative pain. This should be studied further to understand our findings.

Limitations

Several limitations should be noted. First, this was a retrospective study using data from the EHR. It is possible, and likely, that relevant variables were not documented by hospital staff or clinicians and/or patients may not have provided accurate information. Bias of the provider and/or patient may affect willingness to disclose certain history variables such as SUD/OUD and a history of a mental health diagnosis within the EHR. We used the patient's most recent home medication record to calculate MME dosage. There is the potential for possible discrepancies between the current pain medications listed in the EHR versus what patients may have been taking. There is also potential for illicit opioid use, which would not be captured in the EHR. The sample size of patients who received low-dose IV ketamine in the PACU was small; hence, future studies in a large cohort are warranted. Despite these limitations, we examined a consecutive cohort of patients presenting for a scheduled surgical procedure, which is a strength of our study.

Conclusions

To our knowledge, this is the first study to examine preoperative patient characteristics associated with the postoperative administration of low-dose IV ketamine. Two variables had the highest odds ratios associated with low-dose IV ketamine in the PACU. Patients with an MME ≥90/day were 13.26 times more likely to have received low-dose IV ketamine in the PACU and those with SUD/OUD were 4.02 times more likely to have received low-dose IV ketamine in the PACU. Nurses should consider evaluating patients in the preoperative phase of care for MME ≥90/day and those with SUD/OUD, as these appear to be important predictors of low-dose IV ketamine in the PACU. Age in years, between 55 and 71 years, and an outpatient prescription for opioids and methadone were also predictors but were not as robust. However, a larger cohort of patients who received low-dose IV ketamine in the PACU is needed to further develop

and test a preoperative screening tool. Especially given that many PACU patients will not have a history of the variables tested but go on to receive low-dose IV ketamine in the PACU.

Table 1. Definitions of variables examined**.**

Variable	Definition
Demographics	
Age	In years
Sex	Female, Male
Race/Ethnicity (hospital defined)	Asian Black Latinx Multi-Race/Ethnicity White Other
Housing Insecurity (documented in EHR)	No/Yes
Mental Health History (ICD-10 codes)	(ICD-10 F10-69) Mental health diagnosis
	(ICD-10 F10-19) Mental and behavioral disorders due to psychoactive substance use
	(ICD-10 F20-29) Schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders
	(ICD-10 F30-39) Mood [affective] disorders
	(ICD-10 F40-48) Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders
	(ICD-10 F50-59) Behavioral syndromes associated with physiological disturbances and physical factors
	(ICD-10 F60-69) Disorders of adult personality and behavior
Surgical Service	General Surgery Genito Urology Neurological Orthopedics Thoracic Surgery Transplant Vascular Surgery Other (Anesthesia, Breast, Cardiology, Cardiac Surgery, Gastroenterology, Gynecology, Gynecology Oncology, Oral Maxillo Facial Surgery, Otolaryngology Head Neck Surgery, Plastic Surgery, Pulmonary, Radiology, Radiology Interventional, Radiology Neurological)
Pre-operative opioid use history (documented in EHR)	
Opioids	No/Yes
MME ≥90/day	Morphine milligram equivalents (MME) ≥90 or <90 per day
SUD/OUD	No/Yes
Prescription for:	
Opioid	No/Yes
Buprenorphine	No/Yes
Methadone	No/Yes

Acronyms: EHR=electronic health record; ICD=International Classification of Diseases; MME=morphine milligram equivalents; OUD=opioid use disorder; SUD=substance use disorder

Table 2. Demographics and surgical service type among 6,419 patients presenting for a scheduled surgical procedure. Shown is the overall sample and patients who received, or not, low-dose intravenous ketamine in the post-anesthesia care unit.

Variable	Overall	Yes Ketamine	No Ketamine	p-value yes ketamine vs no ketamine
n	6419 (100%)	90 (1.4%)	6329 (98.6%)	
Age Categories				
[18, 41)	1221 (19.0%)	13 (14.4%)	1208 (19.1%)	0.0014
[41, 55)	1290 (20.0%)	19 (21.1%)	1271 (20.1%)	
[55, 63)	1188 (18.5%)	26 (28.9%)	1162 (18.4%)	
[63, 71)	1347 (21.0%)	25 (27.8%)	1322 (20.9%)	
[71, >90)	1373 (21.4%)	7 (7.8%)	1366 (21.6%)	
Sex				
Female	3379 (52.6%)	49 (54.4%)	3330 (52.6%)	0.75
Male	3038 (47.3%)	41 (45.6%)	2997 (47.4%)	
Other (not tested, small sample size)	2 (0.0%)	0 (0.0%)	2 (0.0%)	
Race/Ethnicity (hospital defined)				
Asian	697 (10.9%)	3 (3.3%)	694 (11.0%)	0.017
Black or African American	413 (6.4%)	5 (5.6%)	408 (6.4%)	
Latinx	1062 (16.5%)	8 (8.9%)	1054 (16.7%)	
Multi-Race/Ethnicity	175 (2.7%)	2 (2.2%)	173 (2.7%)	
Other	281 (4.4%)	6 (6.7%)	275 (4.3%)	
White	3791 (59.1%)	66 (73.3%)	3725 (58.9%)	
Housing Insecurity				
No	6393 (99.6%)	89 (98.9%)	6304 (99.6%)	0.31
Yes	26 (0.4%)	1 (1.1%)	25 (0.4%)	
Surgical Service				
General Surgery	961 (15.0%)	16 (17.8%)	945 (14.9%)	0.00068
Genito Urology	338 (5.3%)	2 (2.2%)	336 (5.3%)	
Neurological Surgery	1983 (30.9%)	34 (37.8%)	1949 (30.8%)	
Orthopedic Surgery	1414 (22.0%)	31 (34.4%)	1383 (21.9%)	
Thoracic Surgery	363 (5.7%)	1 (1.1%)	362 (5.7%)	
Transplant	529 (8.2%)	1 (1.1%)	528 (8.3%)	
Vascular Surgery	208 (3.2%)	0 (0.0%)	208 (3.3%)	
Other	623 (9.7%)	5 (5.6%)	618 (9.8%)	

Table 3. Mental health diagnoses documented in the electronic health record in 6,419 patients presenting for a scheduled surgical procedure.

Variable	Overall	Yes Ketamine	No Ketamine	p-value
n	6419 (100%)	90 (1.4%)	6329 (98.6%)	
Mental health diagnosis (ICD-10 F10-69)				
No	5305 (82.6%)	61 (67.8%)	5244 (82.9%)	0.00061
Yes	1114 (17.4%)	29 (32.2%)	1085 (17.1%)	
Mental and behavioral disorders due to psychoactive substance use (ICD-10 F10-19)				
No	6085 (94.4%)	69 (76.7%)	5989 (94.6%)	0.000001
Yes	361 (5.6%)	21 (23.3%)	340 (5.4%)	
Schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders (ICD-10 F20-29)				
No	6401 (99.7%)	90 (100.0%)	6311 (99.7%)	1
Yes	18 (0.3%)	0 (0.0%)	18 (0.3%)	
Mood [affective] disorders (ICD-10 F30-39)				
No	5864 (91.4%)	71 (78.9%)	5793 (91.5%)	0.00019
Yes	555 (8.6%)	19 (21.1%)	536 (8.5%)	
Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders (ICD-10 F40-48)				
No	5814 (90.6%)	77 (85.6%)	5737 (90.6%)	0.1
Yes	605 (9.4%)	13 (14.4%)	592 (9.4%)	
Behavioral syndromes associated with physiological disturbances and physical factors (ICD-10 F50-59)				
No	6341 (98.8%)	89 (98.9%)	6252 (98.8%)	1
Yes	78 (1.2%)	1 (1.1%)	77 (1.2%)	
Disorders of adult personality and behavior (ICD10 F60-69)				
No	6348 (98.9%)	88 (97.8%)	6260 (98.9%)	0.26
Yes	71 (1.1%)	2 (2.2%)	69 (1.1%)	

Table 4. Opioid use history documented in the electronic health record in 6,419 patients presenting for a scheduled surgical procedure.

Variable	Overall	Yes Ketamine	No Ketamine	p-value
n	6419 (100%)	90 (1.4%)	6329 (98.6%)	
SUD/OUD diagnosis				
No	6310 (98.3%)	76 (84.4%)	6234 (98.5%)	<0.0001
Yes	109 (1.7%)	14 (15.6%)	95 (1.5%)	
MME ≥90/day				
No	5517 (85.9%)	20 (22.2%)	5497 (86.9%)	<0.0001
Yes	902 (16.3%)	70 (77.8%)	832 (13.1%)	
Outpatient opioid prescription				
No	5091 (79.3%)	30 (33.3%)	5061 (80.0%)	<0.0001
Yes	1328 (20.7%)	60 (66.7%)	1268 (20.0%)	
Outpatient methadone prescription				
No	6372 (99.3%)	83 (92.2%)	6289 (99.4%)	<0.0001
Yes	47 (0.7%)	7 (7.8%)	40 (0.6%)	
Outpatient buprenorphine prescription				
No	6406 (99.8%)	89 (98.9%)	6317 (99.8%)	0.17
Yes	13 (0.2%)	1 (1.1%)	12 (0.2%)	

Acronyms: MME=morphine milligram equivalents; OUD=opioid use disorder; SUD=substance use disorder

Table 5. Stepwise Model showing variables associated with administration of low-dose intravenous ketamine in 6,419 patients presenting for a scheduled surgical procedure (listed from highest to lowest odds ratio).

Variable	Odds Ratio	2.5 %	97.5 %	p-value
MME ≥90/day	13.26	7.46	24.32	<0.001
SUD/OUD	4.02	2.03	7.53	<0.001
Outpatient Methadone Prescription	2.39	0.93	5.42	0.049
Outpatient Opioid Prescription	1.82	1.09	3.11	0.025
Age (55-71)	1.14	1.02	1.30	0.029

Acronyms: MME=morphine milligram equivalents; OUD=opioid use disorder; SUD=substance use disorder

References

Boenigk, K., Echevarria, G. C., Nisimov, E., von Bergen Granell, A. E., Cuff, G. E., Wang, J., & Atchabahian, A. (2019). Low-dose ketamine infusion reduces postoperative hydromorphone requirements in opioid-tolerant patients following spinal fusion: A randomised controlled trial. *European Journal of Anaesthesiology | EJA*, *36*(1), 8-15. https://doi.org/10.1097/eja.0000000000000877

Carr, D. (2023). Management of acute pain in the patient chronically using opioids for non-cancer pain. *UpToDate*. Retrieved March 17, 2024, from https://www.uptodate.com/contents/management-of-acute-pain-in-the-patient-chronically-using-opioids-for-non-cancer-pain?topicRef=121628&source=see_link

CDC. (2021). *Commonly Used Terms*. Retrieved March 3, 2024 from https://www.cdc.gov/opioids/basics/terms.html

CDC. (2023). *Drug Overdose Deaths*. Retrieved March 14, 2024 from https://www.cdc.gov/drugoverdose/deaths/index.html

Chou, R., Gordon, D. B., de Leon-Casasola, O. A., Rosenberg, J. M., Bickler, S., Brennan, T., Carter, T., Cassidy, C. L., Chittenden, E. H., Degenhardt, E., Griffith, S., Manworren, R., McCarberg, B., Montgomery, R., Murphy, J., Perkal, M. F., Suresh, S., Sluka, K., Strassels, S., . . . Wu, C. L. (2016). Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. *The Journal of Pain*, *17*(2), 131-157. https://doi.org/10.1016/j.jpain.2015.12.008

Cron, D. C., Englesbe, M. J., Bolton, C. J., Joseph, M. T., Carrier, K. L., Moser, S. E., Waljee, J. F., Hilliard, P. E., Kheterpal, S., & Brummett, C. M. (2017). Preoperative Opioid Use is Independently Associated With Increased Costs and Worse Outcomes After Major

Abdominal Surgery. *Annals of Surgery*, *265*(4), 695-701. https://doi.org/10.1097/sla.0000000000001901

Dahlhamer, J. M. (2021). *Prescription opioid use among adults with chronic pain : United States, 2019*. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics.

Dowell, D., Ragan, K. R., Jones, C. M., Baldwin, G. T., & Chou, R. (2022). CDC Clinical Practice Guideline for Prescribing Opioids for Pain - United States, 2022. *MMWR Recomm Rep*, *71*(3), 1-95. https://doi.org/10.15585/mmwr.rr7103a1

Edwards, D. A., Hedrick, T. L., Jayaram, J., Argoff, C., Gulur, P., Holubar, S. D., Gan, T. J., Mythen, M. G., Miller, T. E., Shaw, A. D., Thacker, J. K. M., McEvoy, M. D., Geiger, T. M., Gordon, D. B., Grant, M. C., Grocott, M., Gupta, R., Hah, J. M., Hurley, R. W., . . . Wu, C. L. (2019). American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement on Perioperative Management of Patients on Preoperative Opioid Therapy. *Anesthesia and analgesia*, *129*(2), 553-566. https://doi.org/10.1213/ANE.0000000000004018

El Moheb, M., Mokhtari, A., Han, K., van Erp, I., Kongkaewpaisan, N., Jia, Z., Rodriguez, G., Kongwibulwut, M., Kaafarani, H. M. A., Sakran, J. V., Joseph, B., Ortega, C., Flores, S. L., Gutierrez-Sougarret, B. J., Qin, H., Gao, R., Yang, J., Wang, Z., Gao, Z., . . . Alami, R. (2020). Pain or No Pain, We Will Give You Opioids: Relationship Between Number of Opioid Pills Prescribed and Severity of Pain after Operation in US vs Non-US Patients. *Journal of the American College of Surgeons*, *231*(6), 639-648. https://doi.org/10.1016/j.jamcollsurg.2020.08.771

Florence, C., Luo, F., & Rice, K. (2021). The economic burden of opioid use disorder and fatal opioid overdose in the United States, 2017. *Drug Alcohol Depend*, *218*, 108350. https://doi.org/10.1016/j.drugalcdep.2020.108350

Gan, T. J. (2017). Poorly controlled postoperative pain: prevalence, consequences, and prevention. *Journal of pain research*, *Volume 10*, 2287-2298. https://doi.org/10.2147/jpr.s144066

Gan, T. J., Habib, A. S., Miller, T. E., White, W., & Apfelbaum, J. L. (2014). Incidence, patient satisfaction, and perceptions of post-surgical pain: results from a US national survey. *Current Medical Research and Opinion*, *30*(1), 149-160. https://doi.org/10.1185/03007995.2013.860019

Goldberg, S. F., Pozek, J.-P. J., Schwenk, E. S., Baratta, J. L., Beausang, D. H., & Wong, A. K. (2017). Practical Management of a Regional Anesthesia-Driven Acute Pain Service. *Advances in anesthesia*, *35*(1), 191-211. https://doi.org/10.1016/j.aan.2017.07.010

Gorlin, A. W., Rosenfeld, D. M., & Ramakrishna, H. (2016). Intravenous sub-anesthetic ketamine for perioperative analgesia. *Journal of Anaesthesiology Clinical Pharmacology*, *32*(2), 160-167. https://doi.org/10.4103/0970-9185.182085

Hyland, S. J., Brockhaus, K. K., Vincent, W. R., Spence, N. Z., Lucki, M. M., Howkins, M. J., & Cleary, R. K. (2021). Perioperative Pain Management and Opioid Stewardship: A Practical Guide. *Healthcare*, *9*(3), 333. https://doi.org/10.3390/healthcare9030333

Jain, N., Phillips, F. M., Weaver, T., & Khan, S. N. (2018). Preoperative Chronic Opioid Therapy: A Risk Factor for Complications, Readmission, Continued Opioid Use and Increased Costs After One- and Two-Level Posterior Lumbar Fusion. *Spine*, *43*(19), 1331-1338. https://doi.org/10.1097/brs.0000000000002609

Jouguelet-Lacoste, J., La Colla, L., Schilling, D., & Chelly, J. E. (2015). The Use of Intravenous Infusion or Single Dose of Low-Dose Ketamine for Postoperative Analgesia: A Review of the Current Literature. *Pain Medicine*, *16*(2), 383-403. https://doi.org/10.1111/pme.12619

Jungquist, C. R., Quinlan-Colwell, A., Vallerand, A., Carlisle, H. L., Cooney, M., Dempsey, S. J., Dunwoody, D., Maly, A., Meloche, K., Meyers, A., Sawyer, J., Singh, N., Sullivan, D., Watson, C., & Polomano, R. C. (2020). American Society for Pain Management Nursing

Guidelines on Monitoring for Opioid-Induced Advancing Sedation and Respiratory Depression: Revisions. *Pain Manag Nurs*, *21*(1), 7-25. https://doi.org/10.1016/j.pmn.2019.06.007

Kaafarani, H. M. A., Han, K., El Moheb, M., Kongkaewpaisan, N., Jia, Z., El Hechi, M. W., van Wijck, S., Breen, K., Eid, A., Rodriguez, G., Kongwibulwut, M., Nordestgaard, A. T., Sakran, J. V., Ezzeddine, H., Joseph, B., Hamidi, M., Ortega, C., Flores, S. L., Gutierrez-Sougarret, B. J., . . . Lillemoe, K. D. (2020). Opioids After Surgery in the United States Versus the Rest of the World: The International Patterns of Opioid Prescribing (iPOP) Multicenter Study. *Annals of Surgery*, *272*(6), 879-886. https://doi.org/10.1097/SLA.0000000000004225

Ladha, K. S., Neuman, M. D., Broms, G., Bethell, J., Bateman, B. T., Wijeysundera, D. N., Bell, M., Hallqvist, L., Svensson, T., Newcomb, C. W., Brensinger, C. M., Gaskins, L. J., & Wunch, H. (2019). Opioid Prescribing After Surgery in the United States, Canada, and Sweden. *JAMA network open*, *2*(9), e1910734-e1910734. https://doi.org/10.1001/jamanetworkopen.2019.10734

Murphy, G. S., Avram, M. J., Greenberg, S. B., Benson, J., Bilimoria, S., Maher, C. E., Teister, K., & Szokol, J. W. (2021). Perioperative Methadone and Ketamine for Postoperative Pain Control in Spinal Surgical Patients: A Randomized, Double-blind, Placebo-controlled Trial. *Anesthesiology (Philadelphia)*, *134*(5), 697-708. https://doi.org/10.1097/ALN.0000000000003743

Pendi, A., Field, R., Farhan, S.-D., Eichler, M., & Bederman, S. S. (2018). Perioperative Ketamine for Analgesia in Spine Surgery. *Spine*, *43*(5), E299-E307. https://doi.org/10.1097/brs.0000000000002318

Schwenk, E. S., & Mariano, E. R. (2018). Designing the ideal perioperative pain management plan starts with multimodal analgesia. *Korean J Anesthesiol*, *71*(5), 345-352. https://doi.org/10.4097/kja.d.18.00217

Schwenk, E. S., Viscusi, E. R., Buvanendran, A., Hurley, R. W., Wasan, A. D., Narouze, S., Bhatia, A., Davis, F. N., Hooten, W. M., & Cohen, S. P. (2018). Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Acute Pain Management From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. *Regional Anesthesia & Pain Medicine*, *43*(5), 456-466. https://doi.org/10.1097/aap.0000000000000806

Shen, Y., Bhagwandass, H., Branchcomb, T., Galvez, S. A., Grande, I., Lessing, J., Mollanazar, M., Ourhaan, N., Oueini, R., Sasser, M., Valdes, I. L., Jadubans, A., Hollmann, J., Maguire, M., Usmani, S., Vouri, S. M., Hincapie-Castillo, J. M., Adkins, L. E., & Goodin, A. J. (2021). Chronic Opioid Therapy: A Scoping Literature Review on Evolving Clinical and Scientific Definitions. *The Journal of Pain*, *22*(3), 246-262. https://doi.org/10.1016/j.jpain.2020.09.002

Thomas, A., Borczynski, E., & Bazinski, M. (2022). *Time to ordering and administration of low-dose ketamine infusion in PACU patients with uncontrolled pain: A pilot study*.

U.S. Food and Drug Administration. (2015). *Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS)*. Retrieved from www.fda.gov/downloads/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm311290.pdf

Waljee, J. F., Cron, D. C., Steiger, R. M., Zhong, L., Englesbe, M. J., & Brummett, C. M. (2017). Effect of Preoperative Opioid Exposure on Healthcare Utilization and Expenditures Following Elective Abdominal Surgery. *Annals of Surgery*, *265*(4), 715-721. https://doi.org/10.1097/sla.0000000000002117

Yang, M. M. H., Hartley, R. L., Leung, A. A., Ronksley, P. E., Jetté, N., Casha, S., & Riva-Cambrin, J. (2019). Preoperative predictors of poor acute postoperative pain control: a systematic review and meta-analysis. *BMJ Open*, *9*(4), e025091. https://doi.org/10.1136/bmjopen-2018-025091

Zhou, L., Yang, H., Hai, Y., & Cheng, Y. (2022). Perioperative Low-Dose Ketamine for Postoperative Pain Management in Spine Surgery: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Pain Research and Management*, *2022*, 1-20. https://doi.org/10.1155/2022/1507097

Publishing Agreement

It is the policy of the University to encourage open access and broad distribution of all theses, dissertations, and manuscripts. The Graduate Division will facilitate the distribution of UCSF theses, dissertations, and manuscripts to the UCSF Library for open access and distribution. UCSF will make such theses, dissertations, and manuscripts accessible to the public and will take reasonable steps to preserve these works in perpetuity.

I hereby grant the non-exclusive, perpetual right to The Regents of the University of California to reproduce, publicly display, distribute, preserve, and publish copies of my thesis, dissertation, or manuscript in any form or media, now existing or later derived, including access online for teaching, research, and public service purposes.

DocuSigned by:
Ashley Thomas
544DDB7C3DD84BF...
Author Signature

5/1/2024
Date