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The Role of Ketamine in the Management of Chronic Pain

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by

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Table of Contents

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Abstract

Chronic pain diagnoses are on the rise amongst people within the United States and thought to be an epidemic. It is estimated to affect millions of patients who have suffered trauma, injury, or complications from surgical procedures. The treatment of chronic pain, defined as pain lasting longer than 3 months, can be complicated. There are no definitive treatment options that have garnered a consensus among medical professionals. Treatment usually involves several medical specialties and pharmacological options. Reliance on the use of multiple pharmacological options can cause patients increased hospitalizations, and a reliance on opioids can potentially cause other illnesses due to the treatment side effects. The purpose of this literature review was to evaluate whether ketamine is a suitable option for the treatment of chronic pain. Articles published in the last 15 years that examined its' use in the treatment of chronic pain were evaluated. Articles were eliminated if they involved animal studies or the involvement of pediatric (less than 18 years of age) and/or geriatric patients (over 65 years of age). The systematic review recommends ketamine as an option for patients in the treatment of chronic pain. Evidence suggests a substantial reduction in patients pain scores after the administration of low dose, subanesthetic ketamine. While side effects are common, they are usually mild, and can be easily managed by practitioners and patients. Further investigation is needed via double-blinded placebo-based studies with a larger sample size to fully substantiate the benefits of ketamine in treating chronic pain.

Keywords: ketamine, chronic pain, chronic pain management

Introduction

Chronic pain is a type of pain that lasts long after the injury or illness has subsided or healed. For chronic pain to be identified or diagnosed the pain symptoms need to have lasted for over three months after the initial injury. A patient with chronic pain can be extremely difficult to medically manage and effectively treat their pain. Types of chronic pain can be neuropathic, muscular, mechanical, or inflammatory in nature, and can even be from other processes. These processes can cause changes within the body and can cause the patient long term disabilities. Medical practitioners can have a difficult time in managing, treating and ultimately curing the pain. The purpose of this literature review is to examine whether the administration of Ketamine, a N-methyl-D-aspirate (NMDA) receptor antagonist, can be an effective pharmacological tool in helping treat patients with chronic pain.

Statement of the Problem

Chronic pain is debilitating and has been reported to affect over 76+ million people in the United States alone (Patil, 2012). Chronic pain has a variety of causes including infectious diseases, genetic disorders, trauma, and systemic diseases. Chronic pain can be long-standing, incredibly difficult to treat, and nonresponsive to a myriad of treatment options. This can lead to increased costs for the patient, readmissions to the hospitals, opioid addiction, and secondary illnesses from the attempts to treat chronic pain. There is also a socioeconomic part that is of great importance when discussing chronic pain. It is estimated that one in three Americans are afflicted by chronic pain and that it costs between $560 to $635 billion annually in medical costs (Cohen, 2018). It is thought by some to even be a worldwide epidemic.

Research Question

Is Ketamine a suitable treatment option for the adult population who suffer from chronic pain?

Methods

An in-depth literature review was performed using web-based electronic search databases that included: PubMed, Science Direct and Embase. The article date range was from the last fifteen years (2006-2021) for all databases. Within Science Direct the search was “chronic pain management” AND ketamine NOT depression, which yielded forty-three articles. The PubMed search used was "Chronic Pain"[MeSH Terms] AND "ketamine"[MeSH Terms] and it yielded eighty articles respectively. The window of only fifteen years yielded the most recent medical literature on the topic of Ketamine and chronic pain. This allowed for an in-depth and accurate review of journal articles that were peer-reviewed, systematic reviews, retrospective analyses, and randomized control trials. The articles were reviewed for their bias, research methods and relevance to the topic. Anything with pediatrics and/or geriatrics were eliminated, as the search and PICO question is concentrated to the adult population. Finally, any articles that involved animal studies were removed as well.

Literature Review

An in-depth review has identified that the administration of Ketamine in patients suffering from chronic pain is an acceptable option. Ketamine has been shown to provide analgesia in patients with chronic pain. Within some of the literature there is some evidence and thinking that there could be a dose-response relationship with the administration of Ketamine. For medical practitioners utilizing Ketamine for the treatment of chronic pain, it is imperative to make decisions that are in the best interest of the patient and ones that are evidence-based.

The Pathophysiology of Chronic Pain

Chronic pain has been recognized as a worldwide epidemic by healthcare providers. Unfortunately, chronic pain is often nonresponsive to conventional medical treatments. In 2013, chronic pain was one of the worldwide leading causes of years lost to disability. In fact, four of the top ten causes of disability are related to pain (Cohen, 2018). These causes are low-back pain, migraine, musculoskeletal disorders, and neck pain, with low-back pain leading as the number one cause. Within the United States, the impact of chronic pain is even more distinct as three of the four in the top ten: low-back pain, musculoskeletal disorders, and neck pain have chronic pain components.

Chronic pain and its challenges in treatment have socioeconomic consequences. Patil (2012) stated, "Chronic pain affects over seventy-six million people in the United States. Long-standing intractable pain can be particularly challenging to treat and resistant to multiple treatment modalities" (p. 263). In a 2010 report, the Institute of Medicine estimated that chronic pain afflicts 1 of 3 Americans, costing between $560 billion and $635 billion annually (Cohen, 2018). Over the last 11 years, the annual cost of treating chronic pain has increased, necessitating cost-effective treatment that is managed in a safe and proper manner.

The transition from acute pain to chronic pain occurs when a patient experiences pain lasting over three months. Chronic pain can be categorized in various ways, but the most documented way is by "location" or "type". Central, neuropathic, nociceptive, peripheral, or mixed are common ways to categorize chronic pain as they all incorporate the location and or type of pain. Many experts and healthcare providers consider the distinction between different types of pain to be a continuum, rather than discrete classification of categories (Cohen, 2018).

Chronic neuropathic pain, which is often the predominant category of chronic pain, is caused by lesions on the somatic nervous system which dramatically alter its structure and function. This causes pain to occur spontaneously and amplifies other stimuli, such as noxious and innocuous stimuli. The patient then experiences symptoms such as allodynia, enhanced temporal summation, hyperalgesia, and spontaneous pain when assessed by a medical practitioner. There are neurochemical processes that facilitate the transition from the initial injury and acute pain symptoms to the patient's experience of chronic pain.

The predominant physiologic process in the transition from acute to chronic pain involves phosphorylation and upregulation of the NMDA receptor. The NMDA receptor is a glutamatergic receptor, and its role is to assist with afferent transmission of nociceptive signals. Patients with chronic pain have increased and prolonged stimulation with nociception, which leads to the activation and upregulation of the NMDA receptors within the dorsal horn. This causes prolonged and amplified pain signals to be sent to the brain (Eldufani et al., 2018). Once this amplification occurs, the patient experiences constant pain and other potentially debilitating symptoms. This process is known as central sensitization.

The NMDA receptor can be an ultimate target of treatment, such as by ketamine. The treatment of a patient with chronic pain must be aimed at halting the increased nociceptive inputs to the brain and enhancing the descending inhibition pathway. Ketamine mainly exerts its effects as a NDMA antagonist, which ultimately inhibits the NMDA receptor. This stops the increased nociceptive input to the brain and decreases central sensitization, which can potentially be utilized in the treatment of chronic pain.

Understanding Ketamine

The pharmacological agent ketamine [2-(o-chlorophenyl)-2-methylamino cyclohexanone] has been around for nearly five decades. It is commonly used as an anesthetic agent that can induce general anesthesia while still allowing the patient to maintain their airway reflexes. Ketamine, a derivative of phencyclidine (commonly known as PCP), was initially labeled as CI-581. Two scientists from Parke-Davis (now Pfizer) discovered a new Grinard chemical reaction, which ultimately led to the synthesis of phencyclidine (Cohen, 2018). In early studies analyzing it, ketamine was shown to create a cataleptic state when administered to pigeons. The first administration to humans was in 1964. All twenty volunteers reported symptoms consistent with what would be seen in a dissociative anesthetic state. The dosing range given for the initial administration was 1-2 mg/kg. Ketamine has historically been used as a dissociative anesthetic at higher dosing (1-2 mg/kg) and in this range has analgesic, anti-depressive, psychomimetic and sedation properties.

Ketamine, in the form of ketamine hydrochloride, became available in 1969 by prescription as Ketelar. It was initially administered as an anesthetic during the Vietnam war to soldiers on the battlefield who suffered traumatic injuries. It was fully approved by the FDA in 1970 as the pharmacological agent, Ketamine. Ketamine has a chiral center which allows it to have two enantiomers a S(+)-ketamine and R(-)-ketamine. In Europe, the S(+)-ketamine is only form available and is commonly known as Ketanest. The R(-)-ketamine is a racemic mixture called Ketelar and widely available across the world. Ketelar is what is used in medicine within the United States (Niesters, 2012). S(+)-ketamine is the more potent and longer acting enantiomer as compared to R(-)-ketamine.

Ketamine holds analgesic, antidepressant, and psychomimetic properties due to its actions on numerous pathways. The physiological effects of Ketamine are dose-related. Lower doses are mainly given for its analgesic properties and higher doses are given for its dissociative (general anesthesia) properties. Its primary mechanism of action is as a noncompetitive antagonist at the phencyclidine binding site of N-methyl-D-aspartate (NMDA) receptors residing in the central nervous system (CNS), particularly in the prefrontal cortex and hippocampus where it decreases the frequency of channel opening and duration of time spent in the active, open state (Cohen, 2018). In addition to the known NMDA binding site, ketamine also binds to receptors such as alpha-amino-3-hydroxyl-5-methyl-4-isoxazole propionate (AMPA), gamma-amino-butyric (GABA), L-type calcium channels, kainite, sodium, potassium, opioid receptors (mu, kappa, sigma), muscarinic, and monoaminergic receptors. These too all act upon the central nervous system. The receptor targets that have been identified help us understand that there could be many pathways involved in the clinical effects of ketamine. The activation of the NMDA channel is a major player in cognition, chronic pain, opioid tolerance, and mood regulation. In high doses, ketamine activates the opioid receptors mu, kappa, and sigma and are not reversible by naloxone, whereas opioid drugs like morphine and fentanyl are. Ketamine has been found to activate other non-NMDA pathways that have roles in pain and mood regulation. It has a combination of hypnotic, analgesic, and amnestic effects, which makes it a consummate drug for treating post-traumatic, procedural-related, and chronic pain.

The drug can be administered via intravenous (IV), intramuscular (IM), intranasal (IN), oral (PO), and topical (TD). It is both water and lipid-soluble, which lends itself for quick distribution in the body and an expeditious crossing of the blood-brain barrier. Due to these factors' ketamine has a quick onset, and its effects act within a minute. It can produce central

and peripheral analgesic effects at several locations within the nervous system. There is some newer research that states that Ketamine may have effects on voltage-gated sodium (Na^+) and potassium (K^+) channels, as well as inhibiting dopamine and serotonin receptors.

The administration of Ketamine can have side effects such as increased heart rate (tachycardia), elevation in systolic and diastolic blood pressure (hypertension), increased oral secretions (hypersalivation) and bronchodilation (relaxed airways), due to its stimulation on the sympathetic nervous system (SNS). Its administration can also cause delirium and psychosis, which is more commonly seen in patients that are coming out of the effects of ketamine. These types of reactions are commonly called "emergence reactions" and can be ceased with the administration of a benzodiazepine such as midazolam. Ketamine is metabolized by the cytochrome P450 in the hepatic system into norketamine, hydrooxynorketamine, and dehydronorketamine. It is excreted via the urinary system in the urine. Ketamine's half-life in plasma is approximately 2.3 ± 0.5 hours.

Medical contraindications to the use of ketamine in treating chronic pain are mainly relative and not supported by strong clinically evidence-based research to state any of them are absolute contraindications. Cardiovascular contraindications are unstable angina, poorly controlled hypertension, and high-risk coronary vascular disease. The endocrinological contraindications are thought to be because of ketamine's sympathomimetic effects and are listed as: hyperthyroidism and pheochromocytoma. Severe liver disease is another due to the inability to possibly metabolize ketamine via the cytochrome P450 system. There is a lack of data on the administration of ketamine in pregnant women and its administration should be used with caution in this patient population. Known psychosis and delirium can exacerbate potential

emergence reactions and again caution should be used with its administration in these psychiatric patients but can be treated with a benzodiazepine.

Green (2011) stated "Ketamine exerts its effects by "disconnecting" the thalamocortical and limbic systems effectively dissociating the central nervous system from outside stimulus like pain, sight, and sound" (p. 1). This causes a state of sensory isolation all the while maintaining cardiovascular (CV) stability and maintaining the patient's spontaneous respiration and airway reflexes. Once the effects of ketamine have been reached there is no dose relationship between the maintenance of the patient's airway and the dose given. The only variation to this is if the ketamine is administered too quickly. It is suggested that ketamine be administered over 30 to 60 seconds, if not, there can be some observed respiratory depression and apnea 1-2 minutes after administration if given IV and 4-5 minutes after IM. The potential for apnea is due to the rapid and high CNS levels of the ketamine as the drug passes the blood-brain barrier quickly.

At subanesthetic dosing (<0.5 mg/kg) the plasma concentration will be approximately 70 to 200 ng/ml. Concentrations that are higher than 500 ng/ml are associated with loss of consciousness and surgical anesthesia is around 2000 to 3000 ng/ml. Ketamine has a longer duration in its effects on the treatment of chronic pain as compared to its sedative and hypnotic effects. This is due to the effects of it being mediated by an increase in synaptic connectivity. After more than fifty years of ketamine use a paradigm shift has happened in the management of perioperative and other categories of pain, especially chronic pain and there is an increased interest in ketamine as it makes a true clinical comeback in the affluent world (Mion, 2017).

Ketamine's Role & Effect in Chronic Pain Management

The use of ketamine for chronic pain has been investigated in double-blinded random control studies (RCTs). In several studies, significant reductions in pain during the ketamine

infusions were observed as compared with placebo (Cohen, 2018).

Dr. Martinx Sigtermans has been a leading investigator in the use of Ketamine in recent years. In 2009 Sigtermans et al., published a study that was a double-blinded randomized placebo-controlled parallel-group trial on the use of ketamine and its effectiveness in long-term pain relief for patients suffering from chronic regional pain syndrome type one (CRPS-1). CRPS-1 is a chronic pain syndrome that usually affects its patients after they have suffered trauma or have had surgery to an extremity. The syndrome has symptoms of pain, edema, temperature changes in the skin, color changes in the skin, and hyperhidrosis. This can lead to severe disease, pain, loss of the quality of their life and disability. Sigtermans stated, "There is no evidence that commonly used treatments with opioids, antidepressants, antiepileptics, and sympathetic blockade are effective in CRPS" (Sigtermans, 2009, p. 304). This led them to investigate whether ketamine would be a suitable option.

Patients with a diagnosis of CRPS-1 were recruited for the study as they were referred to their outpatient pain clinic between January 2006 and 2008. For a patient to have a definitive diagnosis of CRPS-1, the patient had to meet criteria set forth by the International Association for the Study of Pain. Patients were excluded from the study if they were less than eighteen years old, had a pain score of less than five out of ten, were currently pregnant or lactating, known to have a strong opioid use, history of increased intracranial pressure (ICP), psychosis, cardiovascular disease, renal disease, or liver disease. Patients were randomly assigned to receive S(+)-ketamine or the placebo (normal saline 0.9%). A physician that had no involvement with the study did the randomization with the assistance of a computer-generated list.

Sigtermans et al., calculated that 25 patients would be needed for the ketamine and placebo groups. This was based on their calculation of a power of 0.80 and a standard deviation

of 2.5. They assumed patients would be lost in follow-up for potentially decline to progress further in the study based on potential side effects, and with this in mind they enrolled 30 patients in each group. A total of 60 patients underwent randomization with the majority being female (80%) and having a disease duration with a median range of 7.4 (0.1-31.9) years. The ketamine infusion was fully carried out in 58/60 patients (96.6%) with two patients terminating the infusion due to severe feelings of being high.

Patients were brought in and admitted to a short-stay unit for five days and IV lines were established. The ketamine infusion was started at 1.2 mcg/kg/min IV on the first day and was titrated at regular set intervals to a max dose of 7.2 mcg/kg/min IV. The rate of the ketamine infusion was increased if the pain relief was not sufficient. The pain relief was monitored based on a visual analogue pain score. If the patient experienced side effects and the patient was accepting of them the infusion would continue and be increased at the set interval. If they were unacceptable, but the patient had pain relief, the infusion was decreased for one interval then increased again. In cases of full pain relief reported by the patient the infusion was not increased and was kept at the rate that achieved full pain relief until the end of the treatment.

Prior to the initiation of the infusion (one week prior) and after the completion of the infusion measurements (eleven-week follow-up period) were taken. The outcome of this study was the reported course of the pain relief over the twelve-week study period. Pain scores were reported by a numerical rating scale (NRS) that ranged from 0 to 10, with zero being no pain and ten being the worst and most unbearable pain the patient could imagine.

Scores at baseline prior to the initiation of the ketamine infusion were 7.20 (SD 1.16) and for the placebo 6.87 (SD 1.43). The NRS were the lowest at the end of week 1 with ketamine being 2.68 ± 0.51 and placebo being 5.45 ± 0.48. It was reported that ketamine managed the

pain during the 12-week study period better than placebo ($P < 0.0001$). "Significant differences in pain reduction between ketamine and placebo were maintained until week 11; at week 12, ketamine's treatment effect lost significance ($P = 0.07$)" (Sigtermans, 2009, p. 307).

The most common side effects during the infusions were noted to be nausea in 63% of ketamine patients versus 17% in placebo patients ($P < 0.001$), vomiting in 47% of ketamine patients versus 10% in placebo patients ($P < 0.0004$), psychomimetic effects in 93% of ketamine patients versus 17% in placebo patients ($P < 0.0001$). There were no reported significant changes in blood pressure or liver functions from the ketamine infusions.

The findings from Sigtermans et al. 2009, suggests that four days of the ketamine infusion may have a clinically significant reduction in pain in patients with CRPS-1 over a 10-week period. There was an observation made slow dissipation of pain relief was due to the short ketamine infusion. Other studies identified where the infusion duration was longer showed a longer ketamine effect on their patients. Sigtermans also noted that even though there was significant pain relief with the ketamine, there was no improvement in the patient's functional status. Sigtermans et al. (2009) stated a longer or repeated ketamine treatments maybe necessary to help facilitate increased activity levels in their patients, thereby improving the functional statuses of these patients. Overall, the study by Sigtermans et al. concluded, "CRPS-1 patients with severe pain treated with four days of continuous low infusion low-dose ketamine using an individualized stepwise tailoring of dosage have a clinically relevant reduction in pain lasting 11 weeks" (Sigtermans, 2009, p. 310).

Lumanauw et al. (2019) published a randomized, double-blind placebo-controlled trial that was conducted from May 2017 to June 2018 that evaluated 106 patients that presented to an emergency department (ED) with complaints of acute on chronic pain and were treated with sub-

dissociative dose of ketamine or a placebo. The study was conducted in an academic teaching facility's ED in Los Angeles County, California which routinely sees 75,000 ED visits per year.

To be included in the study one had to be over the age of eighteen with a known history of chronic pain that presented with a complaint of pain exacerbation. The investigators defined chronic pain as pain in which lasted greater than three months. The patient's pain had to be self-reported as at least 70 mm or higher on a 100 mm visual analog pain scale (VAS). Subjects were excluded if they had a history of psychosis, severe hypertension (defined as systolic > 180 or diastolic > 110), unstable angina, coronary heart disease (CAD), congestive heart failure (CHF), thyroid disease, seizure disorders, or were unable to consent in English or Spanish.

Once the patients presented to the ED they were given a questionnaire to fill out about the cause, duration, and the specific characteristics of their pain. They then rated their pain level and agitation levels on three different VASs. A computer randomized the patient into one of the three groups, one either getting 0.5 mg/kg of ketamine, 0.25 mg/kg of ketamine, or a placebo. The dose of ketamine or placebo was run over 20 minutes via a medication pump. The medication or placebo was mixed by a pharmacist with everyone else being blinded to which option was being used. Each patient was asked to wear sunglasses for the study so that they would not show the investigators if they were having possible involuntary eye movement which can be caused by ketamine and would lend investigators to know the patient had received ketamine.

After the medication or placebo was administered another VAS was filled out by the patient at 20 minutes, 40 minutes and 60 minutes. If the patient's pain was not relieved at one of those time marks, a rescue medication was offered with the approval of the attending ED physician. During the patient's in the study, constant monitoring of vital signs and the onset of

side effects were evaluated. The side effects that were monitored for were, hallucinations, disorientation, agitation, anxiety, dysphoria, nausea, and vomiting. After being discharged from the ED the patients were contacted by phone at twenty-four and forty-eight hours to ascertain their pain levels using a 10-point numerical scale. A rating of ten represented the worst pain the patient could feel with a one being no pain.

Lumanauw et al. (2019) defined a clinically significant pain relief as a decrease in the VAS of at least 20 mm from their initial presentation to the ED. A power analysis using the three groups (0.5 mg/kg, 0.25 mg/kg and placebo) determined that ninety-six subjects would be needed to see a statistically significant difference among the three groups with a power of 90% ($\alpha = 0.05$). It was thought that close to 10% of subjects would be lost during the study due to incomplete data or patient withdraw and a total of 106 patients were recruited.

A total of 106 patients were enrolled from May 2017 to June 2018 and immediately three subjects were ruled out due to not meeting the initial baseline pain VAS score of 70 mm. In the 0.5 mg/kg group there were 35 patients; 36 were in the 0.25 mg/kg group, and 35 in the placebo group with randomization. Several patients in each group were dropped due to for various reasons including patient desire to complete the study, noted side effects, and incomplete patient or study data. This led to 97 patients available for analysis.

The initial pain scores reported were 91.4 ± 8.5 for the 0.5 mg/kg ketamine administration, 93.2 ± 8.9 for the 0.25 mg/kg ketamine administration, and 91.2 ± 9.3 for the placebo administration. Out of the 97 patients, 66 of them reported a significant improvement in their pain, which again was defined as a decrease in their VAS score of 20 mm or more. Ketamine at 0.5 mg/kg and at 0.25 mg/kg were better in pain reduction than the placebo. The patients in the ketamine 0.5 mg/kg group had 25 of 30 (83.3%) with reported significant

reduction, patients in the ketamine 0.25 mg/kg group had 28 of 35 (80%) with reported significant reduction, and patients in the placebo group had 13 of 32 (40.6%) with significant reductions and a p-value of $p = 0.001$. There was no reported statistically significant difference in the reduction of pain between the ketamine dose of 0.5 mg/kg and 0.25 mg/kg, but more adverse events were documented in the ketamine groups. In the ketamine 0.5 mg/kg group 12 patients (40%) and ketamine 0.25 mg/kg group 14 patient (40%) respectively had side effects, but all were tolerable, as compared to the placebo group where only 1 patient reported an adverse event.

The use of rescue medications was higher in the placebo group versus the ketamine groups. For the placebo group seven out of thirty-two patients (23.3%), the ketamine 0.5 mg/kg group twelve out of thirty patients (34.3%) and the ketamine 0.25 mg/kg group seventeen out of thirty-two (53.1%) all received rescue medications respectively, with a p-value of $p = 0.03$.

It was reported that 89 of 96 patients had follow up at 24 and 48 hours post-ED discharged (91.8%). There was an equal distribution in the ketamine 0.5 mg/kg, ketamine 0.25 mg/kg and placebo groups of patients who had follow-up. There was no difference documented in the groups on the median and interquartile pain scores. The ketamine 0.5 mg/kg group had a median pain score of 6 with an interquartile range of 3-8, the ketamine 0.25 mg/kg group had a median pain score of 5 with an interquartile range of 4-8, and finally the placebo group had a median pain score of 5 with an interquartile range of 4-8.

The overall results of the Lumanauw et al. study published in 2019 revealed that ketamine was indeed effective at treating chronic pain as compared to a placebo. The ketamine dosed at 0.5 mg/kg had better results in controlling the pain and needing less rescue medication administrations. There was no reported evidence that the ketamine at either dose resulted in pain

control over 24 to 48 hours post ketamine administration because the pain scores were comparable across all three groups. Both ketamine groups did result in a higher percentage of side effects than the placebo, with the ketamine 0.25 mg/kg group having the highest percentage.

Orhurhu, Orhurhu, Bhatia, and Cohen (2019) performed a meta-analysis on random control trials (RCTs) to evaluate if IV ketamine infusions were useful for pain relief in patients suffering from chronic conditions. Their main method of evaluation to answer their question was a systematic review and meta-analysis. It was conducted using the recommendations of the Cochrane Collaboration and reported in coordination with the Preferred Reporting Items for Systemic Reviews and Meta-Analysis guidelines. The authors searched MEDLINE, Embase, Google Scholar, along with clinical trials from the website www.clinicaltrials.com. Their search time frame was from the inception of each resource to December 16, 2017.

Their review of data was limited to only RCTs that compared the effects of ketamine to a placebo for relieving chronic pain and ones that had a period of follow up for greater than 48 hours. The patient within the RCTs had to have had chronic pain for greater than three months and be over the age of 18. The authors interventions and comparators upon data review were interventions being the bolus and/or infusion of a ketamine dose and the comparators being a placebo. The placebo could be given with or without a form of medical management which could be defined as interventional, pharmacological, physical, and psychological therapies. A primary outcome was recorded as the lowest pain score recorded 48 hours after the completion of the ketamine treatment. This was quantified on a numerical 0-10 scale. Due to their findings that there is a high correlation between a VAS score and a numerical scale all of the VAS scores were taken into a numerical 0-10 scale.

Initially, 696 records were pulled from their search databases and after their first round of screening there were 467 publications. After further evaluation 460 were excluded primarily because they looked at perioperative pain or did not fully meet the outcomes set forth by the investigators. Data from seven RCTs that evaluated 211 patients were subjected to their final meta-analysis. The seven trials evaluated chronic pain syndromes, but there was a wide variation in the type of pain, distribution, and etiology (Orhurhu, 2019). The median of the seven RCTs was 24 patients (range 19-60) in each publication with a median age of 48 years old (range 41-71). Ketamine's infusion duration median for the seven RCTs was five hours with a range of 0.5-100 hours. The median dose utilizing a 70 kg patient as their baseline weight was 0.35 mg/kg with a range of 0.23-0.6 mg/kg being administered.

"Meta-analysis of the data from these trials showed a significant reduction in pain scores favoring ketamine over standard or control comparative treatments (mean difference of -1.83 points, 95% CI, -2.35 to -1.31 points, $P < 0.0001$, $I^2 = 45.5\%$)" (Orhurhu, 2019, p. 244). Of the seven RCTs there were six that had the lowest pain scores within a time frame of 48 hours and two weeks as reported on the numerical 0-10 scale.

The authors also looked at if ketamine and its reduction in pain scores was based on dose dependency. High dose ketamine was defined as a cumulative dose over 400 mg and three of the seven RCTs had the primary outcome with the administration of high dose ketamine and two of the three showed the lowering of pain scores as compared to control groups. The meta-analysis of the high dose ketamine administration data showed a reduction in pain scores versus the placebo (mean difference, -2.11 points, 95% CI, -2.87 to -1.35 points, $P = < 0.000$, $I^2 = 69.2\%$) (Orhurhu, 2019, pg. 244). The data supported that there is a dose dependent relationship with the ketamine and subsequent reduction in pain scores.

This meta-analysis supports the thought that ketamine administration is useful for the treatment of chronic pain. While this may be true, it was shown that the drug's effects do lessen with time and there is a dose-dependent relationship. Dose dependency is not a shocking finding, as normally all analgesic medications like ketamine, morphine, fentanyl, and others, have a dose-response effect when administered. The authors also state that the risk of bias was high in four of the seven trials. Those RCTs did not fully nor adequately describe the procedures for blinding participants and personnel (Orhurhu, 2019). Orhurhu et al. (2019), feel that ketamine is safe to on a case-by-case need to use as an analgesic for patient with chronic pain that is nonresponsive to other treatments.

Two physicians at the University of Chicago Medical Center evaluated if patients treated with IV ketamine infusions could satisfactorily have their pain reduced that was stemming from chronic pain syndromes. Drs. Patil and Anitescu, after obtaining Institutional Review Board approval, performed a retrospective chart review that spanned five years from 2004 to 2009 that evaluated their database at the University of Chicago Medical Center for all ketamine infusions administered over that time frame. All patients had refractory pain for a minimum of six months, which made their pain states fall into a chronic state since the duration was over three months. The patients also had prior diagnostic and treatments to include nerve blocks, peripheral nerve stimulation, decompressions, field blocks, trigger point injections, physical therapy, and psychotherapy, all of which failed in each respective patient.

Their retrospective analysis had several outcome measures they followed such as if the chart had the dose of ketamine administered, duration of the IV infusion, pre and post pain scores based on the VAS, if they patient had long-term pain relief, prior interventions, and any side effects from the ketamine that were noted. It was found that all patients were treated with

midazolam to combat potential psychomimetic effects of the ketamine and ondansetron for its antiemetic properties. In reviewing the chart data 49 patients underwent 369 ketamine infusions at the University Medical Center. They did not include 36 infusions in their report due to lack of data. Complex regional pain syndrome was the diagnosis in 37% (18 patients) and the remaining 63% (31 patients) had diagnoses such as chronic refractory headaches and chronic back pain amongst others.

When a patient would present for their ketamine infusion no changes were made to their medications on the day of the infusion and it was confirmed that no changes had been made in the prior month preceding the infusion. Again, all patients were administered versed and ondansetron prior to the ketamine. The initial dose of ketamine was 0.5 mg/kg given over a time frame of 30-60 minutes and administered via an IV medication infusion pump. If the dose of 0.5 mg/kg was found to be effective in reducing the patient's pain, it was continued in their other infusions. If less than adequate pain relief was found with the initial 0.5 mg/kg dose, then the subsequent doses in the infusions were increased until they reached the highest dose tolerable by the patient that did not elicit side effects. The infusion schedule was set by the pain clinic's protocol at every three to four weeks.

Patil (2012) measured the efficacy of the treatments with pain scores that were charted pre- and post-infusion. The VAS with a numerical value range of 0-10 was used to quantify the patient's pain. A rating of zero stated the patient was having no pain, while a score of ten was listed as the worst pain imaginable for the patient. With each infusion, pain scores were tabulated, and any adverse effects were recorded. The analysis of the data was completed and the level of significance for the retrospective study was set at $P < 0.05$. The mean patient age for

the study was 45 years with a range of 18-68. The majority of the patients at 63.3%, were female, the average weight amongst all of the patients was 83.8 kg (±23.9 kg).

The ketamine infusions were administered for a median time of 38.3 minutes with a range of 30 minutes to 8 hours, with the mean (SD) total ketamine dose administered being 0.9 (±0.4) mg/kg. All the patients reported a VAS scores that had a computed mean of 7.6 (±1.9) prior to the infusions and after the infusions a VAS score median was reduced to 0.9. Every patient also reported a decrease in VAS score of 5.9 (standard error [SE] 0.35) or what equated to a 77% reduction in their pain. Adverse events occurred a total of 35 times in 23 out of 49 (46.9%) patients, with hypertension, hallucinations and sedation being the most common ones identified.

Patil (2012) did not have any reportable data for long-term pain relief for the entire group of the 49 patients they retrospectively evaluated. Even with the lack of this long-term data for the 49, they were able to contact and interview 29 patients (59%). Eight of the 29 patients (27%) stated the duration of the pain relief lasted several hours, 21 patients (73%) said the pain lasted greater than one to two days. Eleven of the 21 that said it lasted greater than one to two days, went on to say that the relief lasted more than three weeks, which was 38% of the total patients interviewed.

The authors recognize their limitations in the retrospective study but do feel that patients with chronic refractory pain when given a sub-anesthetic dose of ketamine, can have their pain significantly reduced. The main limitations for this retrospective study include the lack of follow up data on the long-term relief of the patient's pain. They note that at the time of their study release no large randomized control trials with ketamine have been done for the evaluation of chronic pain relief.

Zerky, Gibson, and Aggarwal (2016), performed a prospective study that was nonrandomized and non-blinded on seventy subjects with chronic nonmalignant pain that presented to their Pain Management Center at the Royal Prince Alfred Hospital in Sydney, Australia, between 2007 and 2012. Each patient was to receive a three to seven day of subcutaneous ketamine, given subcutaneously, in hopes to effectively treat their chronic pain. Patient were not offered ketamine infusions if they had a history of tachycardia, heart disease, psychotic disorders, or uncontrolled hypertension. Zerky et al. collected data and analyzed it based on demographic parameters, site of pain, pain intensity, duration of pain, opioid MEDD (morphine equivalent daily dose), other analgesics used before and after the ketamine infusion, as well as the patient's pain score before and after the infusion. The pain score was based on the numerical rating scale (NRS) which is from zero to ten, with zero being no pain and ten being the worst pain a patient can imagine.

Patients were started on a subanesthetic dose of ketamine given via subcutaneous infusion. The subcutaneous sites utilized for the infusion were identified in each patient where there was an adequate amount of fat and away from joints. The identified the best location to be the upper, anterior chest wall superior to the breast and medially to the axilla. If the patient was thin, they would utilize the abdomen as the location for the infusion. Each injection site was evaluated daily, but they reported the original injection site lasting for up to eight days. This was important to detect early signs of potential inflammation and infection. If there was swelling, bleeding or bruising present, the infusion site was relocated to another part of the patient's body.

The concentration of ketamine was 200 mg in 50 mL of normal saline and started at 4 mg/hr. The rate was titrated daily in 4 mg/h increments until the pain was resolved for the patient had adverse effects from the dose of ketamine. If a patient experienced adverse effects

the rate of the infusion was decreased until they subsided. The maximum infusion rate for the ketamine was set at 32 mg/h by the clinicians. Every eight hours and until the infusion was complete, they recorded and tracked the infusion rate (mL/h), volume infused into the patient (total mL), and the patient's pain score. If the patient was sleeping, they would omit a pain score from their data recording.

The lowest ketamine infusion dose per day was 201 mg/day, the highest being recorded at 526 mg/day, while the mean ketamine infusion dose was measured at 228 mg/day. Infusions were continued for a mean of 6.1 days. Patients who had been taking opioids had their dose decreased by 25% at the start of the ketamine infusion and again decreased by 25% every 24 hours. Clonidine was given to reduce the chance of adverse effects associated with potential opioid withdrawal. At the cessation of the ketamine infusion the patients were followed anywhere from three months to six years and the ones that had a favorable response to the ketamine were given the opportunity for maintenance treatment with sublingual ketamine lozenges. The thought behind the lozenges is ketamine is often administered sublingually to avoid the first-pass metabolism that is commonly seen with orally administered ketamine. Ketamine lozenges were prepared as 100 mg with the dose being given as 25 mg three times a day (TID). This group of patients were followed for a period of three months to two years.

Seventy patients were enrolled with 63% males and 37% females and a mean age of 48.8 for males and 49.8 for females. Out of the initial patients in the infusion study, 18 were lost due to inadequate follow up, which left 52 for the study. The 52 patients had a myriad of diagnosed pain issues to include complex regional pain syndrome, lumbar spinal pain, migraines, trigeminal neuralgia, peripheral neuropathy, and postherpetic neuralgia. A statistically significant reduction in pain was noted during the study. The initial NRS was 6.38 before the ketamine and down to

4.6 after the ketamine ($P < 0.005$). In the patient that had been utilizing opioids as an adjunct there was a noted decrease in their use of opioids after the ketamine infusion. The mean morphine equivalent daily dose was 216 mg/day before the ketamine infusion to 89 mg/day after the ketamine infusions, representing a statistically significant decrease 59% decrease ($P < 0.005$). Regarding the patients who used ketamine lozenges, 31% remained off opioids as opposed to 6% who did not receive the lozenges ($P < 0.005$). The patient group the refused lozenges 11% of them increased their opioid dose and no patient who received the lozenges increased their opioid use. Adverse effects were reported to be mild but common and included lightheadedness (46%), tiredness and sedation (25%), headaches (12%), hallucinations (12%), vivid dreams (8%), and diplopia (2%) and all were easily managed.

The authors noted, despite their positive results, there is no available evidence on the long-term efficacy of subanesthetic, subcutaneous ketamine in the setting of chronic pain (Zekry, 2016). They concluded that chronic pain patients can have significantly decreased pain after ketamine infusions. The limitations identified in this study were robust, as it was a prospective, nonrandomized, and non-blinded study. Patients who received the ketamine lozenges were not randomized in terms of their ongoing pain management. NRS scores could have been affected by opioid use, the patient's current mood at the time of pain scale rating, education, and empathy. While the results were positive, additional double-blinded, randomized control trials are needed to determine the true effect of subcutaneous ketamine and ketamine lozenges in the treatment of chronic pain.

Clark (2020) published an editorial in *Anesthesiology, V. 133,* in July of 2020, outlining an expert opinion on the use of ketamine in chronic pain. They note that ketamine has been through the entire realm of anesthetic practice from an induction agent for general anesthesia, to

an intraoperative adjunct, to an analgesic. Many of the side effects are dose-dependent and quite downplayed. Dr. Clark distinctly expresses that ketamine has dose-dependent side effects that affect CNS and CV systems due to ketamine's sympathetic stimulation. Even with the multiple studies highlighted in the editorial, the belief is, there is limited long-term outcome data available for chronic pain patients who are administered Ketamine.

The consensus is that there is a need for an in-depth assessment for the use of ketamine in treating chronic pain patients. The following list are recommendations stated for the use of ketamine as a treatment modality when patients with chronic pain:

1. "We should develop meaningful data on the risks, with some attention to comorbidities that might predispose patients to adverse outcomes like cardiovascular disease, liver conditions, or substance abuse histories. Patient registries might be a good option here" (Clark, 2020, p. 14).
2. "It would be enormously helpful to research some rational consensus on what defines successful therapy based on pain relief, function, sleep, quality of life, and other measures endorsed for evaluation of outcomes for chronic pain management" (Clark, 2020, p. 14).
3. "It would be helpful to have an empirically supported approach to selecting ketamine dose" (Clark, 2020, p. 14).
4. "Chronic pain management is arguably at its most effective when multidisciplinary…Identifying the optimal combination of ketamine and other therapies will be a difficult but important task" (Clark, 2020, p. 15).

At lower subanesthetic doses (<0.5mg/kg), ketamine has evidence that it can help with acute and chronic pain, decrease the need for opioids, and decrease nausea and vomiting that is

associated with pain management. Patients with chronic pain usually have an inadequacy in their ability to establish the descending inhibition of pain. When ketamine takes effect, it starts up these pathways and causes a descending inhibition of pain. The pathways come from supraspinal sites and stop the dorsal horn neurons that are related to nociception.

Yang (2020) suggests dosing guidelines for the administration of ketamine for chronic pain based upon the route of administration, dosing, indications, bioavailability, and its duration of effect. "Ketamine is a promising treatment for chronic pain. The current understanding of pain pathophysiology highlights ketamine's potential to treat this difficult illness. However, while clinical studies are generally positive, evidence is mostly limited to small RCTs" (Shteamer, 2019, p. 518).

Discussion

Treating chronic pain can be complicated and often involves using a combination of pharmacological options to get a patient's pain under control. Ketamine shows promise in modulating a patient's pain, reducing the need for other drugs and interventions. The data that has been reviewed supports the theory that ketamine can be used as an acceptable option by the medical practitioner to reduce their patient's chronic pain. This is evident by multiple studies that show a reduced pain score from the patient and a reduction of other symptoms.

Lumanauw 2019 and Sigtermans 2009 were the only two studies that were identified and evaluated during the literature review that involved double-blinded and placebo-controlled patients. In the Lumanauw 2019 study that again was double-blinded and placebo-controlled, 66 out of 97 patients were found to have significant improvement in their pain relief. These patients reported an improvement of their VAS score of greater than 20 mm. There were three groups that were examined for the treatment of their chronic pain. Each group received 0.5 mg/kg, 0.25

mg/kg or a placebo respectively. Out of these patients that reported significant pain relief group that got 0.5 mg/kg of ketamine had 83% report a significant reduction in pain, as compared to the other two groups. Rescue medications were needed more often with the placebo group (saline). While this study was performed in the emergency department and follow-up post-intervention was via phone, there was a notable window of pain reduction that only lasted up to 48 hours. The authors did note a dose-dependent relationship to dosing and overall pain relief. With Sigtermans 2009 study, the patients who received ketamine ranging from 1.2 mcg/kg/min to 7.2 mcg/kg/min over the course of their five day stay in the hospital proved to be beneficial in the reduction of their chronic pain. The patients who received ketamine had an average NRS score of 7.20 reduced to 2.68 versus 6.87 down to 5.45 with the placebo group. The significance of the Sigtermans 2009 study was the infusion time was longer five days versus 20 min in Lumanauw's study, as such the duration of pain relief was longer compared to Lumanauw's results. Sigtermans shows pain relief that was clinically significant up to 11 weeks post-infusion, as compared to Lumanauw's, which lasted only 48 hours. A correlation can be possibly made in regard to the length of the ketamine infusion and the duration of pain relief, but certainly more investigation is needed.

Zekry 2016 was a non-randomized and non-blinded prospective study that evaluated subcutaneous ketamine infusions and then as needed ketamine lozenges as needed during a time frame post ketamine infusion. The average infusion of ketamine lasted for 6.1 days and resulted in pain scores being reported (using the NRS) to be reduced from 6.38 to 4.6. Some of the patients who reported a significant reduction initially were given ketamine lozenges to be administered three times a day. The patients who continued to use ketamine to control their pain via the lozenge administration had no use of narcotics to help control their pain. The 6% of the

patients that did receive ketamine infusion but did not get the lozenges ended up taking narcotics to help control their pain. This study was interesting in that it showed ketamine when continued to be used as needed for pain control, could successfully be used to control the patient's pain and reduce the need to narcotics. The remainder of the studies evaluated were meta-analyses or retrospective chart reviews which showed pain reductions lasting anywhere from forty-eight hours to two weeks (Orhurhu, 2019). These meta-analyses had a small number of random control trials and a small patient size, while the retrospective chart reviews only yielded 49 patient charts that they examined (Patil, 2012).

In evaluating the early research to see if ketamine was a viable option in treating chronic pain, adjustments were made to the search methods. The original search within a ten-year time span from 2011-2021 yielded limited data and many of them were meta-analyses. An attempt was made to find singular double-blinded placebo-controlled studies that supported or refuted the research question. After consulting with advisors overseeing this scholarly project, we concluded there would need to be an expansion of the research and evaluate articles out of the ten-year time frame. It was decided upon to look at the data over the past fifteen years, 2006-2011. A new search was conducted as outlined in the methods section, which ultimately yielded several more worthy studies to evaluate. Expanding this search and altering the trajectory of how the data was examined certainly helped find more substantial articles for utilization within this scholarly project. This led to a more solidified and data supported answer to the research question.

Despite the evidence that ketamine can indeed decrease the pain scores in chronic pain patients more double-blinded placebo studies are needed with a larger sample size within the study. Data is needed on evaluating the risks and comorbidities of patients receiving ketamine

and the definition of what is successful ketamine therapy is needed to truly evaluate its effects on chronic pain. Is success defined by solely by a reduction of pain scales or are we to evaluate and incorporate the functional status of the patient post ketamine treatment? Finally, while the data within the literature review has shown dosing around 0.5 mg/kg, a better approach and standardization of dosing is needed with the medical community. Once this further research is performed and evaluated, we can have a clear and consensually approved treatment modality utilizing ketamine for our chronic pain patients. The advancement and expansion in the treatment of chronic pain by the way of ketamine with no doubt help many patients and reduce the need for other treatment modalities and other complicated interventions.

Conclusion

The literature review suggests that using ketamine as a pharmacological intervention in the treatment of chronic pain will reduce pain in this patient population. The evidence from the multiple meta-analysis on random control trials (RCTs), randomized, double-blind placebo-controlled trials, and retrospective analysis of patients during this literature review supports the use of ketamine in treating chronic pain by evaluating the patients pain score prior to and after ketamine initiation. The literature evaluated did not include pediatric or geriatric patients; therefore, these patient populations do not have an answer regarding ketamine's role in the treatment of chronic pain. If clinicians perform a detailed history and physical exam on the patient, then the administration of ketamine in treating their chronic pain can be safe and efficacious. The consensus regarding ketamine dosing is to start at the lowest dose and titrate to the patient's pain levels. Adverse effects are to be treated on a case-by-case basis, and while common, are easily treatable and do not interfere with the pain reduction capabilities of ketamine.

There is a need for further investigation and evaluation of ketamine's role in the treatment of chronic pain. While the definition of chronic pain is set and accepted amongst most medical professionals, a clinically accepted guideline for ketamine in treating chronic pain has yet to be established. Further double-blinded, placebo-controlled studies need to be completed with a larger sample size in them. The additional research and studies can help create defined outcomes for the use of ketamine in chronic pain, such as a consistent dose, route, duration of administration, and evaluation of pain scores when treating these patients. Education is needed among medical providers to expand the use of ketamine past just its use as an anesthetic. This is needed to show its benefits in the treatment of chronic pain. If further studies are as promising as previous ones, then ketamine's role in chronic pain management can be expanded, giving hope and additional treatment options for patients.

Applicability to Clinical Practice

The data within this literature review can potentially guide medical professionals in making sound clinically-based decisions that are evidence-based when deciding to use Ketamine in the treatment of chronic pain. Chronic pain is a complex type of pain that is often difficult to manage and sometimes requires polypharmacy, as well as, involving multiple medical specialties. This type of medical management of chronic pain can carry additional adverse effects or cause other medical problems to manifest within this patient population. By evaluating the efficacy of ketamine in treating chronic pain a medical professional might have a new non-opioid and single pharmacologic intervention at their disposal to help their patients deal with their chronic pain.

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