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Nursing Staff Training on Compounded Intranasal Ketamine for Treatment-Resistant Depression

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Introduction

A large proportion of individuals with major depressive disorder (MDD) do not receive adequate therapy benefits from conventional monoaminergic antidepressant drugs, leading to treatment-resistant depression (TRD) (Di Vincenzo et al., 2021). Treating MDD with two failed antidepressant trials can lead to TRD, a condition wherein patients are twice as likely to be hospitalized in comparison to depressed patients who are not treatment-resistant (Gaynes et al., 2020). MDD and dysthymia are jointly responsible for 46.9 million disability-adjusted life years (DALYs) globally, with each DALY equivalent to a healthy year of life lost to the disability caused by depressive disorders (Vos et al., 2020). In fact, MDD is the single largest contributor to the loss of healthy life, and this contribution has further increased during the COVID-19 pandemic (WHO, 2017). When benchmarked against a total of 369 diseases and injuries, depressive disorders were the 13th leading cause of overall burden and the seventh leading cause of nonfatal burden, globally (Voss et al., 2020). According to the U.S. Food and Drug Administration (FDA) and the European Medicines Agency, TRD is a failure to respond to two or more antidepressant regimens despite adequate dose, duration, and adherence to treatment (U.S. Food and Drug Administration, 2018). It is estimated that TRD affects a range of 6-55% of people receiving antidepressant treatment (Liu et al., 2021). Compared to MDD, TRD is associated with higher rates of chronic medical comorbidities, more frequent and longer hospitalization visits, and impaired functioning in daily activities (Touloumis, 2021; Dibernardo et al., 2018). Additionally, patients with TRD often struggle with substance use disorders, anxiety, and insomnia among other psychiatric concerns, and have a heightened risk of

mortality by suicide compared to patients with MDD alone (Cepeda et al., 2018; Kern et al., 2023). Evidently, the prevalence and burden of both MDD and TRD indicates an imperative need to implement therapies beyond conventional antidepressant medication.

Psychedelic-assisted psychotherapy has become an emerging field of interest in the treatment of mood disorders (Barber & Aaronson, 2022). Among the psychedelics studied, ketamine at subanesthetic doses has an outstanding history in the treatment of depression and has been used in psychiatry since 2000 (Aiken & Newsome, 2023, 01:47). In 2019, the FDA-approved intranasal esketamine spray combined with antidepressants for TRD, with approvals by regulators (U.S. Food and Drug Administration, 2019). Because both the pharmacodynamics and the neurobiological underpinnings of the antidepressant effects of ketamine/esketamine remain unknown (Molero et al., 2018), many clinical providers and nurses may be concerned about utilizing this medication for TRD. There has yet to be an updated global evaluation of the efficacy and tolerability of ketamine/esketamine, as antidepressants seem to be the focus of research by Berman et al. (2000).

Nurses have a role to monitor safety of patients during administration of prescribed medication. In an online survey analyzing the barriers of ketamine administration, healthcare workers reported the most common barrier to ketamine use were adverse effects (42.6%), other practitioners not routinely using the medication (41.5%), lack of evidence (33.5%), lack of familiarity (33.1%), and hospital/institutional policy guiding the indication for use (32.3%) (Bell et al, 2024). Nursing knowledge and comfortability should be present for administration of ketamine to ensure ethical practice and patient safety. Previous ketamine users and their carers reported their perceptions of ketamine and wanted better evidence on the safety of ketamine

after long term use with an emphasis on side effects. Participants were also concerned about healthcare professionals' lack of information about using ketamine as a treatment for depression. Therefore, educating healthcare workers, specifically nursing staff, is not only significant for nursing knowledge and comfortability, but for the safety and care of patients during ketamine treatment.

Despite the FDA's approval of esketamine utilized for TRD and MDD with acute suicidal ideation or behavior, safety risks and the cost of ketamine should be factored into treatment. At the research site, which is an outpatient partial hospitalization program, compounded ketamine intranasal spray is utilized from a compounding pharmacy for a lower cost than utilizing esketamine nasal spray. All compounded ketamine nasal spray products are not FDA-approved, as ketamine differs on a molecular level from esketamine, which is FDA-approved for TRD. Therefore, the FDA announced concern about the increased potential risk of adverse events, misuse, and abuse associated with compounded ketamine nasal spray given the apparent different doses it has been used (FDA, 2019). The partial hospitalization programs in Seattle, Washington utilize an existing protocol for patients diagnosed with MDD or TRD with a need for updated training for nurses who administer this medication intranasally to increase nursing confidence. Updated training on the background and safety of the compounded ketamine nasal spray such as indications and adverse events will be provided for the nursing teams at the residential centers and partial hospitalization program. An updated safety training on this medication is necessary for nursing teams who have the responsibility to uphold the ethical scope of practices before, during, and after administration of the nasal spray.

Background and Significance

Background

It is significant to analyze the epidemiology of MDD and TRD in all demographic groups when considering intranasal ketamine as a promising treatment alternative. MDD is considered one of the largest public health dilemmas in the United States and can lead to many health-related issues if left untreated or poorly treated. The National Institute of Mental Health reported that 16.2 million people (6.7% of the U.S. adult population) experienced a depressive episode in 2016 and determining which demographic groups are evidently a higher risk of suicide may help with treatment (Gaynes et al., 2020). According to the American Psychiatric Association (2013), the prevalence of MDD in 18-29-year-old patients is three times higher than the prevalence in patients over 60 years, and the prevalence in females is 1.5 to 3 fold higher rates than males starting in early adolescence. A retrospective, observation cohort study by Kern et al. (2023) utilized databases on incidences of death due to suicide to determine that suicide rates are higher in younger adults and were more prevalent in men than women. This study also found that rates of suicide were high in patients with TRD which were 0.14 per 100 person-years for patients with TRD and 0.04 per 100 person-years for patients with MDD (Kern et al., 2023). Based on the evidence of suicide rates of younger individuals aged 18-44 with TRD and/or MDD, it appears that ketamine may play a bigger role as a treatment alternative to treatment-resistant depression in men and women.

The role of ketamine is widely known from being utilized as an anesthetic agent for individuals who undergo surgeries to treatment for TRD for short-term antidepressant effects. Ketamine's history, indication, and differences from esketamine are all factors to consider when

utilizing it to treat TRD. In the 1980s, the discovery of the N-methyl-D-aspartate receptor (NMDAR) and its non-competitive inhibition by ketamine prompted advances in mental functioning and memory pathophysiology (Mion, 2017). This is when the NMDAR antagonist, ketamine, was also observed to produce rapid, antidepressant effects on individuals with TRD, making ketamine an alternative option for acute suicidal ideation. The first FDA indication of ketamine in the treatment of psychiatric disorders was the approval of esketamine (Spravato) for TRD in adults. It was shown that Spravato nasal spray and an antidepressant can produce antidepressant effects in patients diagnosed with TRD (Derakhshanian et al., 2021). Ketamine's S-enantiomer, esketamine, is a different version of ketamine that is FDA-approved as an intranasal spray (called Spravato) when used in conjunction with a conventional antidepressant for the treatment of TRD. Spravato and intravenous ketamine are the only two FDA-approved routes of administration, while research on other ketamine derivatives and formulations are still being developed (McIntyre et al., 2023). However, the cost of Spravato nasal spray is not covered by all insurance and can be between $780 to $1,170 for 2-3 sprays (Spravato Prices, n.d.). Although it differs in molecular formulation from the FDA-approved Spravato intranasal spray, generic intranasal ketamine spray works similarly in providing users with rapid, dissociative, and antidepressant effects at low doses of 30-200 mg (Ziegler et al., 2021).

Spravato's safety guidelines are sometimes utilized in the absence of established psychiatric safety guidelines for ketamine. As per the guidelines of Spravato:

> "The nasal spray should be administered intranasally under the guidance of a healthcare provider. Spravato is dosed at 14 mg of esketamine per spray, requiring the administration of 2 sprays per device. Blood pressure should be measured before and

> after administration. Spravato poses a risk for sedation and dissociation following administration; therefore, patients should be monitored for a minimum of two hours following administration of the drug. The most common adverse reactions to the use of Spravato are dissociation, dizziness, nausea, vomiting, sedation, vertigo, hypoesthesia, anxiety, lethargy, increased blood pressure, and increased emotional state" (Jalloh, 2020).

The increased number of nurses at psychiatric clinics reporting advanced knowledge on the background and adverse effects of intranasal ketamine may lead to further opportunities for nurses to be able to administer ketamine safely or increase accessibility for patients receiving this treatment. Thus investigators posed the following question:, "for registered nurses at the psychiatric clinics, does educational training on intranasal ketamine improve nursing confidence on intranasal ketamine safety precautions for clinical practice?"

Some of the therapeutic effects of ketamine may include hallucinogenic experiences that are similar to the effects of hallucinogens, such as psilocybin, MDMA, or LSD, in the use of psychedelic-assisted therapy. Ketamine's hallucinogenic effects are usually portrayed as undesirable "side effects", but are believed to benefit patients with a wide variety of diagnoses (Dore et al., 2019). In a clinical context for the administration of psychedelics, a nurse's role throughout the process is undescribed and under-explored due to the safety and ethical concerns that are associated with administering the psychedelic itself and raises many questions for the nursing profession, leading to a nurses discomfort of working with ketamine. The six competencies required for the training of psychedelic practitioners include empathic abiding presence, trust enhancement, spiritual intelligence, knowledge of the physical and

physiological effects of psychedelics, self-awareness and ethical integrity, and proficiency in complementary techniques, which are all aligned with the values and practices of nurses in palliative and holistic care (Denis-Lalonde & Estefan, 2020).

Review of Literature

In order to develop our training intervention, a literature review was conducted to explore effective educational strategies for nurses interested in ketamine administration and safety monitoring. The significant gap in the literature underscores the necessity for better understanding nursing knowledge and comfort in administering and monitoring these therapies. It also highlights the need for clear guidelines on nursing interventions, safety measures, and therapeutic approaches specific to psychedelic-assisted therapy. By reviewing current findings pertaining to psychedelic benefit and safety, specifically ketamine, and identifying effective methods in literature to educate nursing teams in support of this role, this training will equip nurses with evidence of safe and evidence based patient practice.

The findings across the first three articles recognize the importance of nursing in psychedelic healthcare. The need for enhanced psychedelic education and clear training expectations with standardized guidelines is evident in order to elevate nursing standards in this field. Porta et al. (2024) surveyed Minnesota registered nurses, advanced practice registered nurses, and psychiatric-mental health nurse practitioners, revealing a belief in the significance of nursing in psychedelic healthcare (74.1%). While they showed interest in exploring psychedelic therapy, confidence levels in understanding the benefits (26.5%) and mechanisms of psychedelics (21.2%) were low, indicating a need for more guidance in these areas. Penn et al. (2021) proposed that the lack of support and training in this field may be the result of

inadequate psychedelic education in traditional nursing curricula, and highlighted a need for teaching nurses about psychedelic history, relevant language, and scientific findings in order to improve in their confidence and knowledge of administration. Similarly, Spotswood (2024) noted the absence of formal documentation of psychedelic administration training despite nursing's historical involvement in psychedelic medicine. They proposed clear training expectations, including continuing education, accredited programs, and universally accepted guidelines, to elevate nursing standards in this field. The central theme of these articles highlight nurses' potential in the realm of psychedelic healthcare but emphasize the need for comprehensive education and standardized training to effectively integrate this into nursing practice.

Both traditional lecture and online education modalities have been effective at increasing knowledge regarding ketamine administration and adverse side effects. Several studies utilized an online strategy to ensure effective teaching and comprehension of nursing training material, which was used to guide us in designing our project (Koss, 2021; Lindly, 2021). Koss (2021) suggested that a short evidence-based educational video describing safety and efficacy information of low-dose ketamine for TRD allowed for greater accessibility reaching a larger target audience due to its online delivery. The information for the video was developed by the American Association of Nurse Anesthetists and the American Psychiatric Nurses Association and informed listeners of ketamine’s indications, adverse effects, and safe use. A 15-minute online educational presentation by Lindly (2021) tested mental health professionals’ knowledge on ketamine infusions for TRD, indicating effectiveness of the educational presentation in increasing participant knowledge about the benefits of ketamine after the

post-survey test, compared to a pre-test score of 30%. In addition, traditional lectures have been found to be effective in increasing knowledge of ketamine for nurse student anesthetists (Todorovic, 2016). A similar modality was utilized in this project related to the study by Lindly (2021) in providing nurses an educational presentation on intranasal Ketamine to assess nursing knowledge with pre-survey and post-surveys.

Although research on ketamine's sustained and long-lasting antidepressant results are limited, a considerable body of evidence can be utilized to inform nurses on adverse effects and safety monitoring (Lindly, 2021). Studies by Lapidus et al. (2014), Peters et al. (2023), and Short et al. (2018) demonstrated the tolerability and effectiveness of intranasal ketamine at various doses, with minimal and short-lasting side effects. The most notable adverse effects among these articles included increases in dissociation, elevations in blood pressure and heart rate, headache, dizziness, and blurry vision, which typically resolved shortly after dose administration (Lapidus et al., 2014; Peters et al., 2023; Short et al., 2018). Active monitoring of these adverse effects can provide nursing facilitators with structured monitoring parameters, such as the systematic assessment for treatment emergent effects (SAFTEE) instrument and the ketamine side effect tool (KSET) (Lapidus et al., 2014; Short et al., 2018). Peters et al. (2023) suggests patient monitoring through utilization of the Glasgow Coma Scale with blood pressure and heart rate checks before ketamine administration, after administration, and every 30 minutes until baseline readings are achieved (usually within 90 minutes). If patients experience a systolic blood pressure over 140 mmHg or a diastolic blood pressure above 90 mmHg prior to ketamine administration, the medication should be held (Peters et al., 2023).

Ketamine education in nursing includes environmental safety factors that can promote a patient's comfort during administration. Safety recommendations include having patients stay on site for administration with a 2-hour post-intervention monitoring period, providing a quiet space with noise-cancellation headphones, and observing the patient 1:1 or 1:2 by trained personnel (Knyahnytska et al., 2022). Based on the following recommendations, as well as further guidelines from Commonwealth of Pennsylvania (2020), we incorporated the following into our training education intervention: consistent blood pressure, heart rate, pulse oximetry, and neurological checks, as well as actively asking patients for any new onset of dizziness, nausea, headache, and pain throughout ketamine administration. Additionally, we recommended the implementation of respiratory intervention equipment, such as non-rebreather face masks, to be better prepared for a potential case of respiratory depression. These safety measures and environmental factors stress the importance of adequate education for nurses in mitigating potential risks, as the successful implementation of ketamine relies not only on the medication's efficacy, but also on the confidence of the nurses in employing these interventions and understanding potential adverse events.

Methods

Design

The design of this project is a quality improvement quasi-experiment in which the investigators determine the impact of the educational intervention based on the outcomes of the pre- and post-surveys. The primary objectives of this DNP project are to measure the

effectiveness of the educational intervention on nursing confidence regarding intranasal ketamine, its safety precautions, and documentation process.

Setting

The setting for this project is a mood and anxiety treatment center that provides different levels of care to adults and children/ adolescents ages 10 and older of all genders with a range of mental health conditions, such as major depressive disorder, generalized anxiety disorder, OCD, mood disorders, eating disorders, and trauma-related disorders. The treatment center is divided into two locations, which include a residential treatment center and a partial hospitalization program. The partial hospitalization program provides patients with the ability to develop lifelong recovery skills in a structured, supportive environment. This program is offered 7-8 hours per day and consists of roughly 15-20 patients that attend 5 days in the week. This is the location where intranasal ketamine is administered; patients from residential and the partial hospitalization program who are prescribed ketamine come to the partial hospitalization program for administration and monitoring. The residential treatment center is for medically stable patients who require a supportive 24-hour treatment environment due to higher acuity of mental health conditions. The approximate capacity of the treatment center is up to 30 patients between the adults and children/adolescents floor. There are a total of 7-8 providers between both locations, in which two providers prescribe and monitor ketamine administration. One of the more prominent ethical considerations for this project involves teaching nurses about a formulation of ketamine that is not currently FDA-approved but is more accessible to the population by financial means. The facility in which this DNP project will be implemented

has been utilizing compounded intranasal racemic ketamine for several years under strict safety and administration guidelines, and has observed great efficacy in its patient population. Lastly, IRB has approved the project with no risk of harm to nursing staff that are participants in this study.

The treatment center accepts private insurances, such as Blue Cross/ Blue shield, Aetna, Cigna, Kaiser Permanente of Washington, Premera, United Behavioral Health, Regence, and more. The investigators of this project are registered nurses at the partial hospitalization program who administer intranasal ketamine to physician approved patients with treatment-resistant depression.

The training was virtually held through Microsoft Teams during an optional one-hour nursing meeting. The link to the meeting was set up by the investigators and sent out to all nurses via email 1-2 weeks in advance. Participants were invited to attend via messages sent through email and Microsoft Teams. There was no monetary incentive to attend and participate in the study.

Participants

A convenience sample of registered nurses currently employed at the mood and anxiety treatment center attending the nursing meeting was taken. Meetings are typically attended by 15 nurses out of 20 from the residential and partial hospitalization program. Exclusions included anyone not attending the meeting part of the treatment center's nursing team. Background knowledge or nursing experience in ketamine was not necessary for participation.

The researchers have created a comprehensive consent form highlighting the risks and benefits of participation in the study. This information will be given to all eligible participants of the study prior to the start of the project. Participants have been verbally reminded and are aware that declination will not impact employment status, and all information obtained is confidential and anonymous. Participant privacy is protected through providing separate links to the pre-test and post-test that do not require identity or personal information and data is stored in an encrypted and password protected cloud server. Investigators have discussed with participants that the research is not conducted by the employer, but results will be utilized to improve guideline information for the employer's use. This training did not grant any approval or certification for nurses to conduct ketamine administration, as further hands-on training would be needed.

Intervention Plan

The findings of this research will be used to improve the project site's current ketamine guidelines and flow of documentation, and to ensure safe patient practice. As a quality improvement project, the data collection procedure included self-report via survey before and after an educational session on ketamine safety precautions and interventions. The whole session from beginning to end lasted approximately 30-40 minutes. The educational information on the powerpoint was aligned with the questions on the questionnaire.

The authors working in the mood and anxiety center presented to the nurses and developed the online survey. Before providing the pre-survey link, implied consent was discussed by the investigators to inform participants of this research being optional, the protection of data, and their participation being anonymous. Investigators initiated the project

with a 5-10 minute pre-survey, a 15-minute presentation followed by a 5-minute question/answer time, and a 5-10 minute post-survey. The pre-survey was sent to participants as a link, the PowerPoint presentation was viewed by all participants and attendees through the Microsoft Teams “sharing screen” feature, and the post-survey was sent as a separate link through Qualtrics.

Measures

Investigators developed 10 Likert-style quantitative survey questions to assess nursing knowledge on the safety interventions of administering intranasal ketamine. The quantitative survey used for the pre- and post-test included questions on the nurses’ perceived competency to recognize the adverse effects of ketamine, identify respiratory depression of a patient, potential contraindications, and charting assessments with six answers ranging from “strongly disagree”, “somewhat disagree”, “neither agree nor disagree”, “somewhat agree”, “strongly agree”, and “prefer not to answer.” The survey results will be provided to the stakeholders for an option to revise the guidelines for more thorough understanding if the majority of the participants answer with a “strongly disagree” or a “somewhat disagree” on a specific topic.

Data Analysis

The response data was collected and stored using the Qualtrics survey platform. The data was then exported to Microsoft Excel to calculate descriptive statistics for the pre and post-survey scores, utilizing the “Analysis Toolpak” add-in. A histogram was created to visualize the distribution comparisons of the pre-survey and post-survey mean scores per each question.

A one-sample t-test has been performed to determine whether there is a one-tailed difference between the pre-test and post-test scores. Then, a p-value will be obtained to accept or reject the null hypothesis. We hypothesized that participants will gain confidence for ketamine safety practice from pre-survey to post-survey with higher scores on the post-survey.

Sustainability Plan

The training powerpoint will be accessible to the stakeholders for nursing use in the future. It may or may not be updated by the stakeholders, which is dependent upon ketamine use guidelines within the facility. The facility does not have any burdens in utilizing this training except for the use of time during nursing meetings. Continuation of this topic may include the specific method of administration of ketamine with steps, pictures, and/or videos for nurses in training. The facility may or may not decide to make this training mandatory for nurses who are expected to administer ketamine in the partial hospitalization program. Upon finalization of the research, the opportunity to continue ketamine training will be provided to Seattle University DNP students working at the study facility.

Results

Outcome

Of the 8 nurses who attended the meeting, 7 survey responses were obtained for the pre-test, and 8 survey responses were obtained for the post-test, resulting in a 88% and 100% response rate, respectively. The post-survey results included eight counts in which a participant

did not fill out or submit a pre-survey, which is accounted for through an unequal variance T-test. Quantitative data from these results were analyzed using an unequal variance one-sided T-test to compare pre-survey scores with post-survey scores, as well as comparing individual questions.

Overall, participants mean confidence in their knowledge increased following the intervention as evidenced by the difference between the mean pre-survey score and the mean post-survey score ($t = 2.45$, $p = 0.02$).

Figure 1

Pre-survey and Post-survey Mean Scores per Item

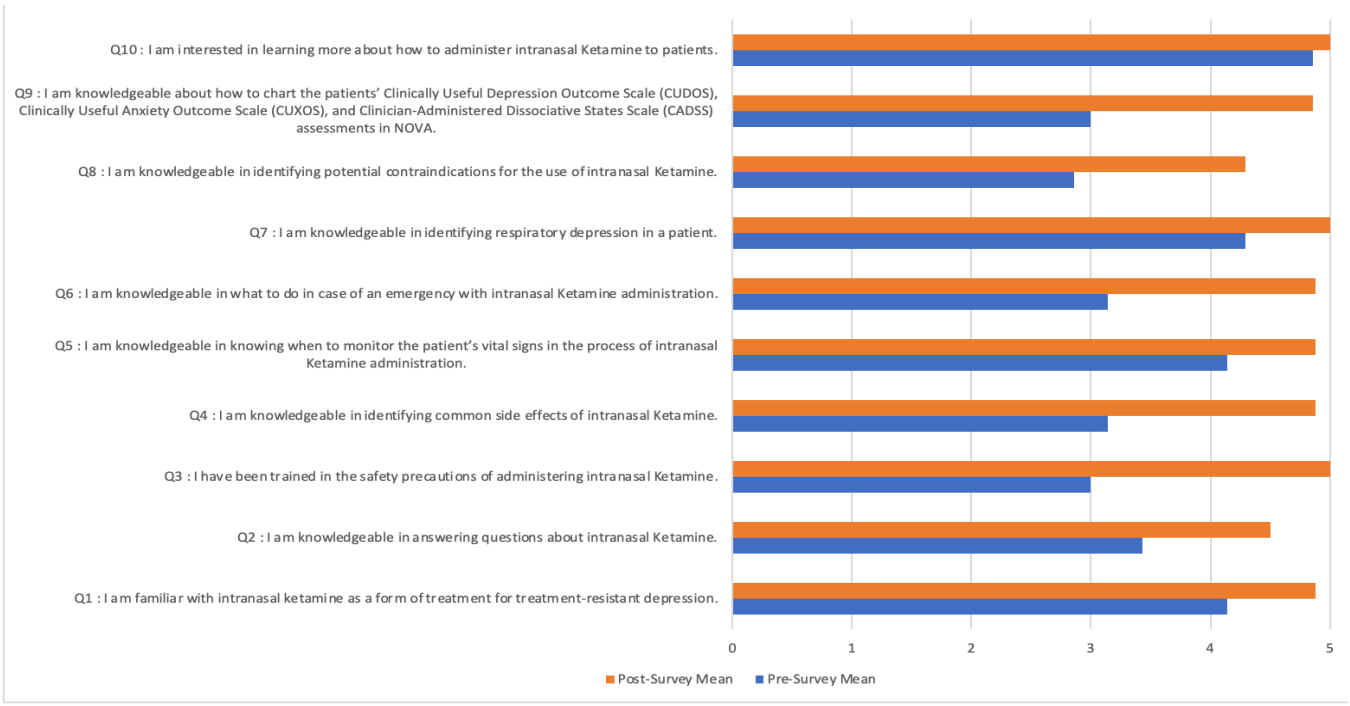

Table 1

Descriptive Statistics of Nursing Ketamine Education

Item	Pre-survey Mean (SD)	Post-survey Mean (SD)	t-value	p-value
1. Familiarity	4.14 (1.07)	4.88 (0.35)	1.76	0.061
2. Answering questions	3.43 (0.79)	4.5 (0.53)	3.21	0.0047
3. Training for safety	3 (1.41)	5 (0)	3.75	0.0047
4. Identifying side effects	3.14 (0.9)	4.88 (0.35)	4.89	p<0.001
5. Monitoring vital signs	4.14 (1.07)	4.88 (0.35)	1.76	0.061
6. Emergency protocol	3.14 (1.57)	4.88 (0.35)	2.86	0.014
7. Identifying respiratory depression	4.29 (0.49)	5 (0)	3.83	0.0043
8. Identifying contraindications	2.86 (1.21)	4.29 (0.49)	2.91	0.011
9. Charting assessments	3 (1.73)	4.86 (0.38)	2.76	0.017
10. Interest in administration	4.86 (0.38)	5 (0.53)	0.78	0.22

Note. N= 7 pre-survey, N=8 post-survey.

Seven items showed significant increases in pre/post-survey confidence after the educational session, including knowledge of answering questions about ketamine, training on safety precautions, emergency protocol, charting assessments, and identification of side effects, contraindications, and respiratory depression (Table 1). Three items, regarding familiarity of intranasal ketamine as a form of treatment for patients with TRD, when to monitor for vital signs during administration, and interest in administering intranasal ketamine, did not show significant increases.

In the pre-survey, the majority of participants answered “neither agree or disagree” (approximately a score of 3) in questions 3, 4, 6, 8, and 9 indicating room for improvement in knowledge with these specific topics (Figure 1). The greatest change in survey scores is shown in question 3 in which participants were asked if they were trained on the safety precautions of administering ketamine ($p=0.0047$). Prior to the intervention, participants were most confident in their existing knowledge on questions 1, 5, 7, and 10 in the pre-survey, regarding familiarity of intranasal ketamine, when to monitor vital signs during administration, identification of respiratory depression, and interest in administering ketamine (Figure 1). In the post-survey, the majority of the participants strongly agreed with improvement in knowledge for all questions, except when asked about identifying potential contraindications with intranasal ketamine, ie medical conditions or medications that may contraindicate with the use of intranasal ketamine, which averaged a mean score around 4 (Figure 1).

Discussion

This project question is intended to answer: can education on the safety and monitoring of intranasal ketamine in patients improve nursing knowledge for future administration of this medication? The data analysis indicated that the education presentation was successful in increasing nursing knowledge in providing education on intranasal ketamine for seven out of the ten survey items. This project shows that educating nurses on intranasal ketamine promotes nurses to develop skills that may be utilized for future ketamine administration to patients with treatment-resistant depression.

The three question items that did not show a statistical significance in change over the pre-test and post-test include topics on familiarity, monitoring time of administration, and interest in learning more about administration of ketamine in the future. The items on familiarity with intranasal ketamine and interest in learning more are expected to not show a statistical change due to nurses having previous knowledge on this treatment and having existing interest in learning about ketamine which was indicated at high mean score in the pretest. The one item that did not show a statistical significance in nursing knowledge included the topic on when to monitor the patient's vital signs during the administration of intranasal ketamine. The potential reasons for this not portraying a change could have been due to lack of thoroughness in content and may have drawn confusion to nurses as to when they are required to take vitals during administration. The lack of visual representation/ demonstration on this topic could be a reason for less understanding, as nurses may need an in person demonstration of monitoring vitals during an administration of ketamine. The question with the lowest

post-survey mean score indicates a lesser understanding of potential contraindications of ketamine which may be due to a lack of thorough explanation of pre-existing medical, psychiatric conditions or medications that contraindicate with the use of ketamine.

The seven items that showed a statistical change indicated the understanding of topics discussed during the presentation, and successful use of technology to deliver continuing education, as the slides may be utilized for future education purposes amongst the site's nurses. The confidence in mean scores before the educational presentation show that nurses may be unaware of safety precautions, training on safety, emergency protocol, identifying contraindications, and charting assessments in which training before administration deems necessary for confidence of knowledge in clinical practice. The lack of awareness on the need for continuing education with newer clinical practices remains a bigger issue in nursing which may be related to time, finances, participation, or staffing in most employment facilities. In a systematic review on the enablers and barriers of e-learning in healthcare, 9 of the 24 papers reported that e-learning is a time, cost, and labor-intensive approach, with learners reporting lack of technology skills (Regmi & Jones, 2020). A recent literature review identified that self-motivation, relevance to practice, preference for workplace learning, strong enabling leadership, and a positive workplace culture are key factors to enable or optimize the impact of nursing continuing development (King et al., 2021). Therefore, providing nurses a preference of topics that are relevant to psychiatric practice, such as interventional psychiatric treatments, complementary and alternative medicine, or psychedelic related interventions, may have a positive impact on motivational factors.

Newer psychiatric treatments, such as transcranial magnetic stimulation, which is FDA approved for MDD and TRD, is provided at this outpatient clinical site and may be a future topic of continuing education for nurses interested in learning more about interventional treatments for TRD. Based on results of increased confidence in knowledge of intranasal ketamine, it is suggested for future educational training to be offered for nurses to stay up to date on the latest interventions for psychiatric treatment. The implication of further continuing education through the use of technology includes ease of access and addresses the short-term and long-term education goals of nurses, all which may affect the quality and satisfaction of a nurse in their job. Other outpatient psychiatric clinics that want to adopt a training or presentation related to the safety or administration of intranasal ketamine may view that an online presentation method was utilized in this project and showed improvement in confidence amongst nurses, and may be replicated for nursing confidence, knowledge, or competency.

The findings of this research aligned with similar studies, such as Lindly (2021) which also utilized an online educational presentation to assess comfortability on Ketamine knowledge, resulting in higher post-test scores than pre-test scores. The second study by Koss (2021) sharing a video to social media platforms on the safety and efficacy of ketamine use in TRD was evaluated by its number of views, shares, likes, and comments in which participants indicated that viewers found the video informative and encouraging. A suggestion for future research includes an interactive method of ketamine administration training for nurses to improve comfortability and/or confidence in administering intranasal ketamine to patients with TRD. A literature review was conducted on teaching nursing students evidence-based education in which an interactive style of learning is often preferred because the method facilitates

student learning (Horntvedt et al., 2018). Interactive methods include small group work, reading quizzes, workshops, or case scenarios that may involve interactions amongst the participants. For future ketamine administration and safety training, a suggestion may be to continue utilizing an online powerpoint, but to include a component of interactive methods to further engage participants. A tougher item that nurses did not feel completely confident in, such as contraindications with ketamine, could be taught with a case scenario in which participants are encouraged to collaborate.

Barriers

Barriers contributing to the project's implementation included the virtual format of the training. While convenient, this posed some challenges regarding participant engagement and interaction, potentially altering the effectiveness of the educational intervention and participant retention of information. The lack of a physical or monetary incentive, as well as the time of the meeting occurring past work hours limited participation rates, as only 8 out of 20 nurses attended the meeting. Additionally, the small sample size limited the statistical power of the findings, making it harder to generalize the results to a larger population. The one-hour time constraint of the session only allowed for a superficial introduction to ketamine, and the absence of hands-on training limited the practical application of the knowledge gained, which further prompts the necessity for a second educational session.

The project showed slides of information through words, but did not show live demonstrations of safety methods conducted which may be a barrier for nursing knowledge or retention in the future. For future educational purposes, a video or demonstration of safety

protocol or administration with intranasal ketamine is suggested to fulfill a wider range of educational methods for nursing knowledge.

Strengths

One of the notable strengths of this project was its quality improvement quasi-experimental design, as it allowed for a practical assessment of the educational intervention's impact through pre- and post-surveys. This design was particularly suitable for evaluating changes, and the outcomes were desirable in indicating overall nursing knowledge and confidence improvement. The participants' lack of concerns or difficulty with survey completion and following instructions also highlighted the comprehensivity and ease of the design. The project setting in a specialized mood and anxiety treatment center ensured that the intervention was implemented in a relevant and controlled environment, and the inclusion of staff from both residential and partial hospitalization programs increased the diversity and representativeness of the sample. The use of virtual training via Microsoft Teams ensured accessibility and convenience for participants The significant improvement in post-survey scores indicated the training's success in enhancing nursing knowledge and confidence in administering intranasal ketamine safely.

Limitations

The limitations relating to this research should be acknowledged. Firstly, the study was conducted within a specific treatment center, potentially limiting the generalizability of the findings to other healthcare settings. The reliance on a convenience sample of nurses who

chose to attend the optional training session introduced selection bias, which also limited the generalizability of the findings. Additionally, we acknowledge response bias through the self-reported survey data, as participants may have provided socially desirable responses or overestimate their competency. The lack of a control group in the quasi-experimental design presents challenges in establishing causality between the educational intervention and observed changes in nursing confidence, as other uncontrolled variables may have influenced the outcomes. While efforts were made to ensure the comprehensiveness of the training session, the study did not include follow-up assessments or additional hands-on training to evaluate the long-term impact on nursing practice. Lastly, the study's reliance on Likert-style survey questions may have limited the depth of qualitative insights into nurses' perceptions and past experiences with intranasal ketamine administration. Despite these limitations, the study provides valuable insights into the potential benefits and areas for improvement in nursing education and practice related to ketamine safety precautions and documentation processes.

Implications for Advanced Practice Nursing

The results of this project demonstrated that targeted educational interventions can significantly enhance nursing knowledge and confidence in administering intranasal ketamine, including safety precautions and documentation processes. This improvement is crucial for advanced nursing practice as it empowers nurses to provide more effective and safer care for patients undergoing this treatment. The increased confidence and competence among nurses can lead to better patient outcomes, particularly for those with treatment-resistant depression. There is room for improvement on topics such as identifying potential contraindications for the

use of intranasal ketamine which may be revised or updated by future investigators or the stakeholders. Recommendations for providing education on ketamine's pharmacological content will be provided to stakeholders for future investigators.

Sustainability

The project aims to focus on all levels of education that nurses have obtained in order to educate the team on a treatment that is becoming more common in psychiatric facilities. Before this training, there was not a formal presentation-based training conducted before nurses were assigned to administer ketamine. Thus, this training may lead nurses into gaining interest with background safety knowledge before in-person training. This training upholds the nursing responsibilities of controlled substance administration, and ensures that nurses continue to practice safe patient care with regards to ketamine administration. This also benefits the patients by granting them assurance and confidence in the training and skills of the nursing staff.

All in all, this project highlights the importance of improving nursing continuing education by including psychedelic-assisted therapy curriculum that may benefit patients with complex psychiatric disorders. This educational presentation is considered a tool that supports nurses in building up confidence to learn about alternative treatments. As a plan to uphold sustainability, investigators will make the educational material on ketamine safety accessible to nurses in outpatient or inpatient clinics who may not be trained in the administration of this

medication. Not only does this encourage safety for the short-term and long-term health of patients, but also advocates for nurses who want to practice in an ethical clinical environment.

Dissemination

The dissemination of this project includes providing a submission to be shared with the outpatient clinic's nursing leadership team as an additional nursing training component for intranasal ketamine safety guidelines. The results of the project will also be shared and presented to the Seattle University College of Nursing Faculty. The dissemination of this information would ensure nurses at the outpatient clinic and associated clinics are up to date on evidence-based safety guidelines and monitoring with ketamine. We hope that education on safety interventions will encourage associated clinics to consider compliance with relevant laws and guidelines on ketamine, to reduce the risk of legal and regulatory issues that can affect their clinic's long-term operation. All nurses from different backgrounds will be considered when writing and disseminating safety and monitoring protocols, by utilizing basic English vocabulary, expanded abbreviations, and definitions for complex words. Overall, this study has a goal to benefit and improve the organization's quality of care, nursing knowledge, and patient outcome and satisfaction.

Conclusion

Due to the novelty of psychedelic use and acceptance in psychiatry, there is a lack of standardized guidelines and education on ketamine's use for treating TRD. The focus of this project was to present an educational intervention about intranasal ketamine to nurses working

at a mood and anxiety center, with the goal of improving participants' perceived knowledge on ketamine's safety. A pre-survey, powerpoint presentation, and post-survey were provided to the nursing team with quantitative analysis showing significant increases in nursing knowledge on seven out of the ten items on the survey. Recommendations will be provided to the facility for future educational methods on items that did not show significant change from pre-survey to post-survey scores.

The project provides evidence to support the importance of nursing-specific treatment-related education, which aims to improve the outcome of nursing experience, safety, and patient access to treatments. Continuing education holds a significant place for nurses to be able to learn and practice modern, up to date, and novel interventions. This project may be redesigned with a live demonstration of ketamine administration as an improved way to train nurses. The additional component of a live demonstration or video of administration may provide more inclusive and effective teaching for those who are visual learners, and thus further increase nurses' readiness, comfort, and confidence in administration.

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Appendix A:

Pre-survey and post-survey questionnaire for nursing training on compounded intranasal ketamine

Please indicate how much you agree or disagree with the following statements:

1. I am familiar with intranasal ketamine as a form of treatment for treatment-resistant depression.
a. 1- Strongly disagree
b. 2 - Somewhat disagree
c. 3 - Neither agree nor disagree
d. 4 - Somewhat agree
e. 5 - Strongly agree
f. Prefer not to answer

2. I am knowledgeable in answering questions about intranasal Ketamine.
a. 1 - Strongly disagree
b. 2 - Somewhat disagree
c. 3 - Neither agree nor disagree
d. 4 - Somewhat agree
e. 5 - Strongly agree
f. Prefer not to answer

3. I have been trained in the safety precautions of administering intranasal Ketamine.
a. 1 - Strongly disagree
b. 2 - Somewhat disagree
c. 3 - Neither agree nor disagree
d. 4 - Somewhat agree
e. 5 - Strongly agree
f. Prefer not to answer

4. I am knowledgeable in identifying common side effects of intranasal Ketamine.
a. 1 - Strongly disagree
b. 2 - Somewhat disagree
c. 3 - Neither agree nor disagreed. 4 - Somewhat agree
e. 5 - Strongly agree
f. Prefer not to answer

5. I am knowledgeable in knowing when to monitor the patient's vital signs in the process of intranasal Ketamine administration.
a. 1 - Strongly disagree
b. 2 - Somewhat disagree
c. 3 - Neither agree nor disagree
d. 4 - Somewhat agree
e. 5 - Strongly agree
f. Prefer not to answer

6. I am knowledgeable in what to do in case of an emergency with intranasal Ketamine administration.
a. 1 - Strongly disagree
b. 2 - Somewhat disagree
c. 3 - Neither agree nor disagree

d. 4 - Somewhat agree
e. 5 - Strongly agree
f. Prefer not to answer
7. I am knowledgeable in identifying respiratory depression in a patient.
a. 1 - Strongly disagree
b. 2 - Somewhat disagree
c. 3 - Neither agree nor disagree
d. 4 - Somewhat agree
e. 5 - Strongly agree
f. Prefer not to answer

8. I am knowledgeable in identifying potential contraindications for the use of intranasal Ketamine.
a. 1 - Strongly disagree
b. 2 - Somewhat disagree
c. 3 - Neither agree nor disagree
d. 4 - Somewhat agree
e. 5 - Strongly agree
f. Prefer not to answer

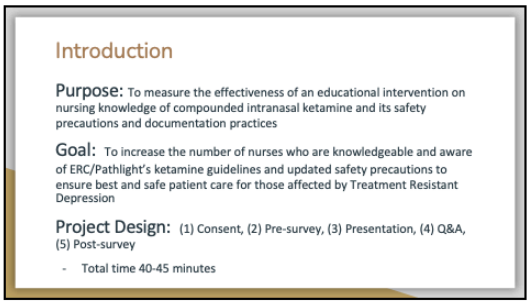
9. I am knowledgeable with how to chart the patients' Clinically Useful Depression Outcome Scale (CUDOS), Clinically Useful Anxiety Outcome Scale (CUXOS), Beck's Depression Inventory (BDI), and Clinician-Administered Dissociative States Scale (CADSS) assessments in NOVA.
a. 1 - Strongly disagree
b. 2 - Somewhat disagree
c. 3 - Neither agree nor disagree
d. 4 - Somewhat agree
e. 5 - Strongly agree
f. Prefer not to answer

10. I am interested in learning more about how to administer intranasal Ketamine to patients.
a. 1 - Strongly disagree
b. 2 - Somewhat disagree
c. 3 - Neither agree nor disagree
d. 4 - Somewhat agree
e. 5 - Strongly agree
f. Prefer not to answer

Appendix B:

Nursing Staff Training on Compounded Intranasal Ketamine for Treatment Resistant Depression

1



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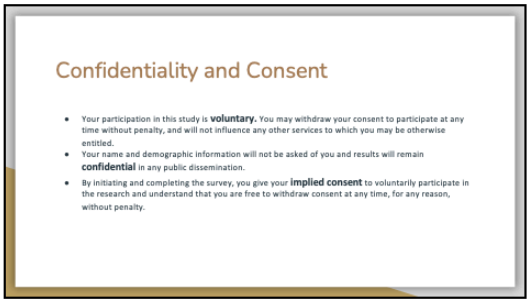

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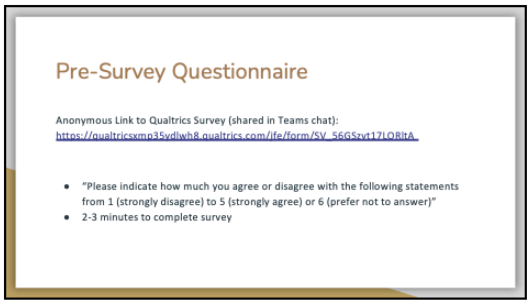

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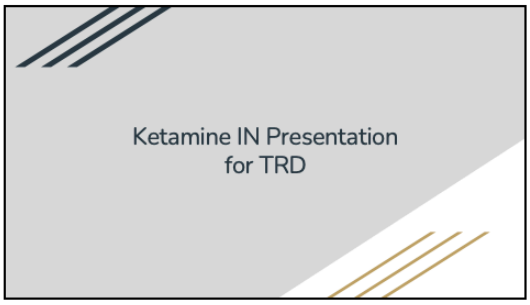


6

Background of Ketamine IN (Intranasal)

Mechanism of Action: NMDA Receptor Antagonist, Racemic (mixture of S and R enantiomers), differ from Esketamine (S-Ketamine)

- Triggers glutamate production → brain forms new neural connections → creates new pathways → positive thoughts

FDA Indication: Anesthesia

Off-label use: Treatment resistant depression (TRD), chronic pain, severe agitation (in the ICU)

Utilized as a short-term rapid antidepressant for treatment resistant depression (failure to respond to or tolerate ≥ 2 different antidepressants)

Dosage: Lower subanesthetic dosing than what is used in surgery (0.5 - 1.0 mL)

Onset of action: 10-15 minutes

Methods: IV, IM, and IN Spray

7

Dosing + Administration

- Formulation: 100 mg/mL liquid solution
- Dosing
  - Initial dose of 0.45 mL for patients below 60 kg (133 lbs) or 0.60 mL for patients above 60 kg (133 lbs)
  - Psychiatric provider will adjust dosing based on
    - CUDOS/CUXOS scores
    - Side effects
    - Presence of nystagmus on exam
    - Remission of primary symptoms
  - Dosing can occur every 3-7 days for up to 4 weeks
  - After 4 weeks, provider to reassess maintenance dosing vs plan to discontinue
- Administration Tools:
  - 1 mL syringe
  - Nasal Mucosal Atomization device (MAD)
- Environment
  - 8th Floor Mount St. Helen Room Cabrini PHP
  - Quiet, low stimulation

8

Before Ketamine Initiation

- Prescribing physician needs to ensure that a medical exam has been completed within 30 days of first dose
  - Medical Hx includes: allergies and past drug rxns, current meds, any diseases/disorders/medical abnormalities, prior hospitalizations, hx of head trauma/seizures, pertinent family hx, medical review of systems, recent labs (CBC, CMP, Urinalysis) and EKG
- **Contraindications** providers should screen for:
  - Pts with uncontrolled/unmanaged high blood pressure, hx of substance misuse within past 6 mo, schizophrenia and other psychotic disorders, non-adherence with tx recommendations, poorly controlled glaucoma, abnormal electrolytes and EKG, breastfeeding/pregnant, unstable medical illness, hx of head trauma/LOC/seizures, symptomatic orthostasis, resting pulse rate below 60, concurrent use of naloxone, concurrent use of high doses of benzodiazepines

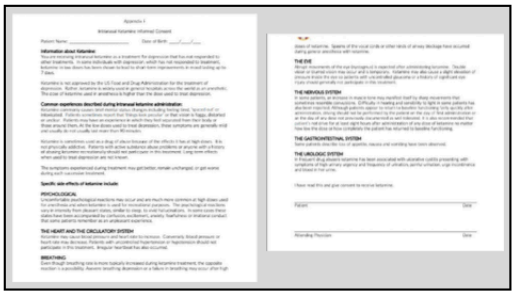
9

First Dose + First Admin of Increased Dose:

1. Prescribing physician responsible for providing
   a. Ketamine Medical Clearance Form
   b. Ketamine informed consent
   c. Education on ketamine plan + dosing expectations
   d. Medication order in NOVA
2. RN will provide the following documents
   a. Pre-administration Clinically Useful Depression Outcome Scale (CUDOS)/Clinically Useful Anxiety Outcome Scale (CUXOS) form
   b. Clinician-Administered Dissociative States Scale (CADSS)
   c. Monitoring flow sheet
   d. Post-administration CUDOS/CUXOS form
3. Encourage fasting before ketamine administration to prevent GI distress (nausea/ vomiting)
4. Educate patient on common side effects and to bring PRN ginger candy, tylenol, or ibuprofen (clear with provider first)
5. First time dose: psychiatrist/ prescriber is needed for first 15 minutes of administration

10

11



12

Ketamine IN Monitoring

Session duration: 2 hours (120 minutes)

Duration of Treatment: Approx. 3-8 sessions over the course of several weeks, twice a week (two days in between)

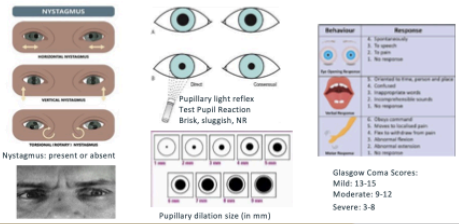
Pre-administration (baseline) and Post-administration: BP, HR, O2 Sat, Temp, pain scale, SE (nausea, headache), LOC (Glascow Coma Scale), Pupillary light reflex and pupillary dilation size, nystagmus (involuntary, rapid, repetitive movement of the eye)

Monitoring Schedule:

- First Dose + First Administration of increased dose: before administration, 15 min, 30 min, 60 min, 90 min, and 120 min after administration
- Previously tolerated doses: Before administration, 60 min, 120 min

13

Ketamine IN Monitoring - Eye Exams



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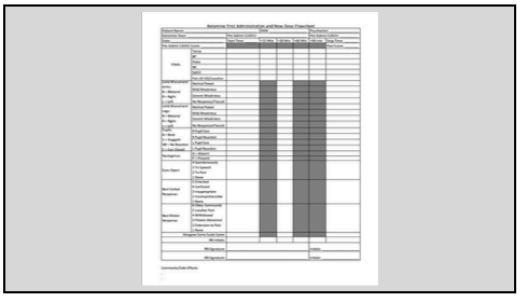

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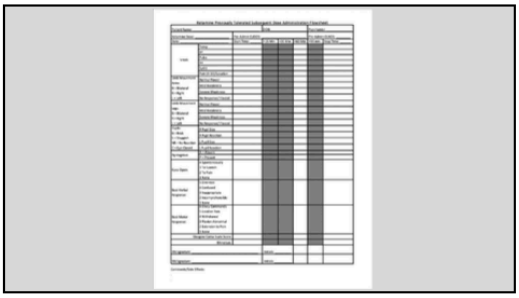

16

Side Effects + Interventions

Most common side effects: dizziness, nausea, confusion, blurred vision, poor coordination, feeling "spaced out", increase in blood pressure

Interventions:

- **Nausea:** provide patient's ginger candy, if it persists, contact prescriber
- **Headache**: provide patient's Tylenol or ibuprofen
- **Dizziness:** Provide patient water and to sit down for 10-15 minutes
- **Re-experiencing memories or traumas:** If pt is distressed, validate and ground
- **Minimal dissociation ("out of body" experience that resolves post administration):** Educate pt that this is to be expected. If continues post admin, stay with pt in room until it resolves

Patients should NOT drive for a minimum of **8 hours** after assessed as returned to baseline

17

Emergency Safety Precautions

Serious but rare adverse effects: Respiratory depression, hemodynamic effects, LOC, dissociation/psychotomimetic effects

- Sx of **respiratory depression**: Rapid, shallow breathing, shortness of breath, RR 8-10 breaths per minute, lips/fingernails turning blue.
  - Call ambulance/ provider right away, **bag mask valve**
- Sx of **hemodynamic effects**: BP over 180/120 mmHG, bradycardia (below 60 bpm) and tachycardia (above 120)
  - **Call provider at BP 160/90, HR < 60 bpm, HR > 120 bpm,** assess w/ provider and call ambulance right away
- **Severe Level of Consciousness** in Glascow Coma Scale (motor, verbal, eye opening response)
  - Call ambulance/ provider right away
- **Dissociation/ psychotomimetic effects** (altered senses, depersonalization/ hallucinations, delusions
  - Call provider
  - Can be unsettling for patients, utilize grounding techniques, touch/see/feel
  - Resolving post administration (varies in hours)

Bag Valve Mask utilized for **respiratory depression**

18

Ketamine IN Monitoring

Session duration: 2 hours (120 minutes)

Duration of Treatment: Approx. 3-8 sessions over the course of several weeks, twice a week (two days in between)

Pre-administration (baseline) and Post-administration: BP, HR, O2 Sat, Temp, pain scale, SE (nausea, headache), LOC (Glascow Coma Scale), Pupillary light reflex and pupillary dilation size, nystagmus (involuntary, rapid, repetitive movement of the eye)

Monitoring Schedule:

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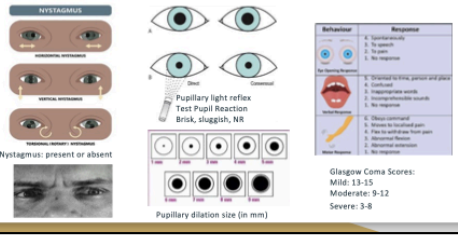
- Previously tolerated doses: Before administration, 60 min, 120 min

13

Ketamine IN Monitoring - Eye Exams



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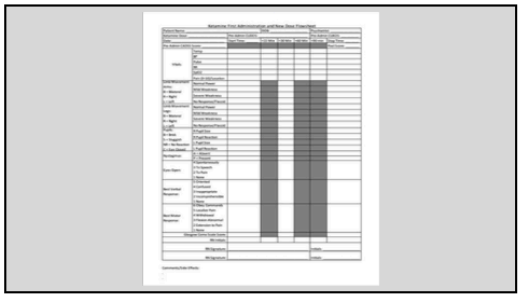

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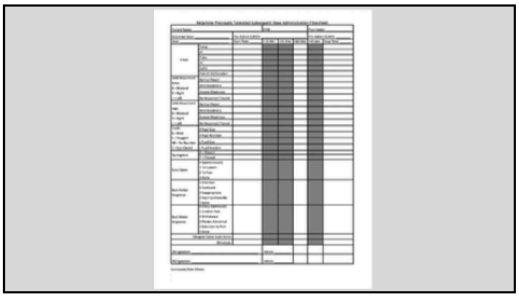

16

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- **Headache**: provide patient's Tylenol or ibuprofen
- **Dizziness:** Provide patient water and to sit down for 10-15 minutes
- **Re-experiencing memories or traumas:** If pt is distressed, validate and ground
- **Minimal dissociation ("out of body" experience that resolves post administration):** Educate pt that this is to be expected. If continues post admin, stay with pt in room until it resolves

Patients should NOT drive for a minimum of **8 hours** after assessed as returned to baseline

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Emergency Safety Precautions

Serious but rare adverse effects: Respiratory depression, hemodynamic effects, LOC, dissociation/psychotomimetic effects

- Sx of **respiratory depression**: Rapid, shallow breathing, shortness of breath, RR 8-10 breaths per minute, lips/fingernails turning blue.
  - Call ambulance/ provider right away, **bag mask valve**
- Sx of **hemodynamic effects**: BP over 180/120 mmHG, bradycardia (below 60 bpm) and tachycardia (above 120)
  - **Call provider at BP 160/90, HR < 60 bpm, HR > 120 bpm,** assess w/ provider and call ambulance right away
- **Severe Level of Consciousness** in Glascow Coma Scale (motor, verbal, eye opening response)
  - Call ambulance/ provider right away
- **Dissociation/ psychotomimetic effects** (altered senses, depersonalization/ hallucinations, delusions
  - Call provider
  - Can be unsettling for patients, utilize grounding techniques, touch/see/feel
  - Resolving post administration (varies in hours)

Bag Valve Mask utilized for **respiratory depression**

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