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A Learning Module in Post-Traumatic Stress Disorder (PTSD) and the Use of 3,4-Methylenedioxymethamphetamine (MDMA) Assisted Psychotherapies in Patients who have PTSD and Other Alike Disorders

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A Learning Module in Post-Traumatic Stress Disorder (PTSD) and the Use of 3,4-Methylenedioxymethamphetamine (MDMA) Assisted Psychotherapies in Patients who have PTSD and Other Alike Disorders

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TABLE OF CONTENTS

ABSTRACT

Background: Patients who have PTSD are particularly vulnerable to inefficient treatment modalities and subsequent lifelong suffering. Multiple studies have exposed these inefficiencies in conventional therapies and established a potentiality for MDMA use during psychotherapy sessions in this patient population. Ketamine represents an anesthetic with a similar psychedelic profile to MDMA that is used in current clinical settings.

Context: Mount Sinai Medical center is a 672-bed hospital in Miami Beach, Florida, where the Miami Beach Anesthesiology Associates (MBAA) group provides anesthesia services. Many procedures requiring anesthesia are carried out to a vast patient population, many of which are patients with PTSD and associative symptoms of depression.

Objectives: The objective of the Evidence-Based Learning Module is to expand CRNA knowledge of PTSD and the use of 3,4-Methylenedioxymethamphetamine (MDMA) assisted psychotherapies in patients who have PTSD and other similar disorders.

Methods: A pre-implementation survey assessed the providers' initial knowledge of PTSD, including current treatment modalities and overall inefficiencies, and the pharmacology and history of MDMA. A virtual educational intervention then followed this. When completed, anesthesia providers were redirected to a post-intervention survey to establish the growth of knowledge.

Results: Overall, there was an improvement in provider knowledge following the education intervention. There was no change regarding the likelihood of researching MDMA further on the CRNA's own time.

Conclusions: Currently, there exist many insufficiencies in the treatment of patients with PSTD. During the perioperative period, an area of heightened vulnerability for this population, a universal standard of care or anesthetic plan specific to patients with PTSD is lacking. The educational intervention provided was effective in improving anesthesia provider knowledge of PTSD and MDMA.

Keywords: post-traumatic stress disorder, 3,4-methylenedioxymethamphetamine, ketamine

INTRODUCTION

The epidemiology of post-traumatic stress disorder (PTSD) includes many traumas and is frequently associated with major depressive disorders (MDD). Despite several symptoms, varying traumatic experiences, and a high PTSD or MDD frequency specific to this subgroup, effective treatment modalities remain scarce. This proposes its own unique set of challenges in each facet of the medical field, as patients with PTSD or MDD have reported higher rates of comorbid disorders. Resultantly, this also includes a heightened need for medical and surgical services.[1]

The first-line treatment for PTSD is psychotherapy.[2] According to the American Psychological Association's (APA's) 2017 clinical practice guidelines, this involves Trauma-Focused Cognitive Behavioral Therapy (TF-CBT) and Eye Movement Desensitization and Reprocessing (EMDR).[2] Even with patient compliance with these suggested modes of care, PTSD persists as a lifetime disorder lacking total resolution in numerous cases.

The use of pharmacological therapy designated in PTSD management is limited. The only medications currently approved by the Food and Drug Administration (FDA) for PTSD are the selective serotonin reuptake inhibitors' (SSRIs') sertraline and paroxetine hydrochloride.[3] Of patients receiving SSRI therapy, a study by Thal et al[4] concluded that only 20 to 30 percent had reported any improvement. In a 2015 systematic review (SR) and meta-analysis by Hoskins et al[5], SSRIs were found to have a "minor effect" in reducing symptoms associated with PTSD in patients. The insufficient evidence existing around PTSD and depression treatment efficacy points to a demand for additional research.

Description of the Problem

3,4-Methylenedioxymethamphetamine (MDMA) is a substituted phenylethylamine first synthesized in 1912 by the German pharmaceutical company Merck.[3,6] There is a widespread misconception of MDMA's origin, with many reviews incorrectly citing it as evolving from the development of an appetite suppressant. Following a systematic analysis of Merck's archive

documents, however, MDMA was ultimately recognized by the company as a precursor to a hemostatic substance.[6]

In the 1970s, MDMA's use in combination psychotherapy catalyzed communication between patients and therapists. As MDMA was being utilized in this manner, published reports suggested a specific value to its use with patients who experienced trauma and concurrent depression. Before this method obtained momentum, MDMA also gained popularity as the main constituent of the psychedelic drug Ecstasy. Subsequently, in 1985, MDMA was ruled as a schedule one substance in the United States (US), making its use in therapy illegal and difficult to research clinically.[7]

Ketamine shares a similar pharmacological history of trials and tribulations. Produced initially with the intent of forming a shorter-acting analog of phencyclidine, Ketamine's psychedelic and dissociative properties also contributed to it gaining a reputation for recreational use.[8] Stimulatory effects of the drug predominate at lower doses, inducing hallucinatory disassociations as well as an overall distortion of time and space that, much like MDMA, may be appreciated in non-clinical settings.[8]

The properties that make Ketamine a proper anesthetic, such as cardiorespiratory stability while maintaining sedation and analgesia, have simultaneously limited its usefulness as a monotherapy agent. For example, even at subanesthetic doses, dissociative symptoms and psychological effects may be too intrusive and not tolerated by patients. Following the introduction of propofol in the 1970s, Ketamine's use as an anesthetic grossly grew out of popularity.[8]

Presently, the rising use of Ketamine in the clinical setting has facilitated an increasing body of research. Ketamine represents an anesthetic with similar psychedelic propensities to MDMA currently utilized to manage treatment-resistant depression (TRD). This subsequently better establishes its effectiveness as a modality that can be expanded to patients with PTSD who regularly suffer from associated depression. Despite working on differing neurological receptors,

ketamine and MDMA yield comparable effects, and both may serve as catalysts to therapy.[9] Suppose higher-level research existed on the specific use of MDMA in settings where Ketamine has been nearly used exclusively. In that case, MDMA could become a valid alternative for treatment.

Background

PTSD diagnoses are challenging to establish secondary to the heterogenicity of symptom presentation. The need to explore past trauma often drives patients away from seeking medical help, making the true prevalence of PTSD a challenging value to capture. According to the National Comorbidity Survey Replication (NCS-R), the lifetime incidence of PTSD in adult aged samples in the United States and Canada ranges from 6.1 to 9.2 percent.[10] In the more recent 2012-2013 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) study, lifetime prevalence was concluded to be higher in women (8.6%) than men (4.1%).[11] Among individuals with lifetime PTSD, only 59.4 % sought care with an average of 4.5 years lapsing from diagnosis to initial treatment.[11] More up-to-date research is needed to capture the scope of this issue in complete accuracy.

PTSD is a prevalent mental health disorder with longstanding effects and a high rate of reoccurrence. PTSD contributes to reduced life quality and the development of comorbid conditions such as depression, obesity, hypertension, additional mental health conditions, and suicidality.[7] Total resolution using traditional treatment modalities is an uncommon clinical phenomenon.

The handling of patients presenting with PTSD and their concomitant depressive symptoms also offers unique challenges to medical providers. Diagnosed and undiagnosed PTSD in patients undergoing surgery, for example, demonstrate a higher rate of emergence delirium (ED).[12] ED is an experience characterized by altered mental perception, including confusion, disorientation, illusion, agitation, and occasional violence following anesthesia's cessation.[12] This

is a costly incidence associated with prolonged length of hospital stay and increased patient morbidity and mortality.

PTSD and TRD are underappreciated clinical issues. Individuals specifically suffering from previous traumas often do so silently, as exploring them through therapeutic interventions may exacerbate symptoms. Additionally, medical providers rarely address the difficulties that exist around treating PTSD and its associative conditions. Instead, they are often viewed as individual experiences or isolated occurrences, contributing to the poor response rate to first-line interventions.

MDMA's overarching stigma of a drug primarily of recreational custom has limited its useability in clinical investigation and psychotherapy.[7] To establish the worth of MDMA in practice, its current reputation must be overcome by collecting data from studies with high levels of evidence. Reproducible examinations extending into phase 3 trials would rebuild MDMA's standing and significantly increase its possibility of use clinically.

The need for enhanced treatments for PTSD and its associative symptoms of depression is supported by the disease's overall prevalence in everyday medical practices and poor patient outcomes with current strategies. The use of MDMA in a clinical setting, though proven both safe and effective in various RCTs, requires additional evaluation before being taken seriously as a potential treatment option. A review of the current evidence will support future studies' indication and strengthen MDMA's usefulness in this manner, offering a hopeful future solution to patients.

Systematic Review Rationale

The rationale behind this SR is a foundation of inadequate pharmacotherapies that have demonstrated reliable effectiveness in treating chronic PTSD or antidepressant-resistant (ADR). Concerning an overall low response rate to first-line interventions, further investigation reveals an area of medicine with a limited collection of research. When considering the commonality of ADR and PTSD, this is an unjustifiable reality. Furthermore, the medications approved by the

FDA, paroxetine, and sertraline, were outlined over two decades ago. The search or development of novel medications has since remained stagnant.

Objectives of the Systematic Review

The purpose of this SR is to identify available evidence and evaluate each study's findings on the efficacy of MDMA-assisted psychotherapy in the treatment of chronic PTSD. Following Johns Hopkins' appraisal scale, the author then extrapolated level one and two evidence, later establishing a direct comparison to Ketamine.[13] The review also aims to assess a potential new adjunct to traditional PTSD and TRD management. This SR includes the highest-quality double-blinded RCTs, SRs, and meta-analyses that serve to answer the proposed PICO (i.e., patient population, intervention or issue of interest, comparison intervention or group, and outcome) question.[13] The findings will ultimately be used to establish a basis of safety and efficacy, supporting MDMA-assisted psychotherapy and expanding the knowledge of its use to anesthesia providers. This SR answered the PICO question: "(P) In adult patients with chronic PTSD and associative symptoms of depression, (I) how does the use of MDMA-assisted psychotherapy (C) compare to ketamine-assisted psychotherapy (O) in the reduction of symptoms?"

METHODOLOGY OF LITERATURE REVIEW

Search Strategy and Sources

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was used as a guide throughout the search.[14] This review used the electronic databases MEDLINE (ProQuest), Excerpta Medica Database (EMBASE), and Cumulative Index of Nursing and Allied Health Literature (CINAHL) to find relevant articles. Keywords and concepts were extracted from the PICO question and implemented into each database's search table. The words "post-traumatic stress disorder" OR "PTSD"; AND "ecstasy" OR "MDMA" OR "3,4-Methylenedioxyamphetamine" OR "methylenedioxymethamphetamine" were implemented into the search database and yielded 59 articles from CINAHL, 124 from MEDLINE, and 176 from

EMBASE. The keywords “post-traumatic stress disorder” OR “PTSD”; AND “ketamine” was then implemented into the same databases to find comparison articles. This yielded 43 articles from CINAHL, 183 from MEDLINE, and 290 from EMBASE. Duplicate articles were removed, and the remaining were initially screened according to publication dates, focusing on the last 5 to 10 years. The investigators organized the selected articles via EndNote into folders entitled “CINAHL Ketamine”, “CINAHL MDMA”, “EMBASE Ketamine”, “EMBASE MDMA”, “MEDLINE Ketamine”, and “MEDLINE MDMA”.

Study Selection and Screening of Evidence

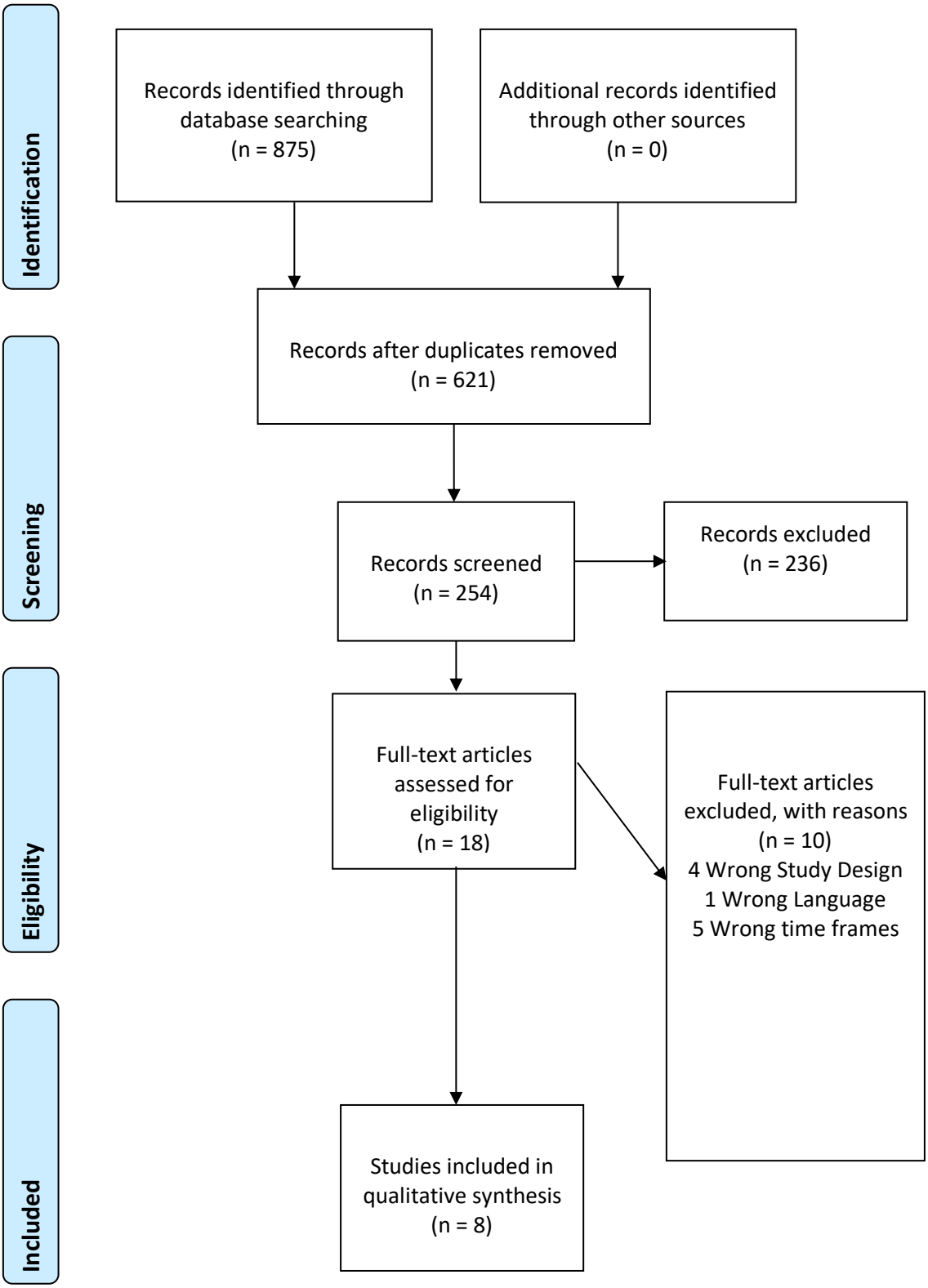
Following consideration of the level of evidence, two investigators conducted a screening based on the title and abstracts in relation to the preliminary PICO question. The remaining studies were then critically appraised in a full-text analysis. Inclusion criteria comprised of: articles published from 2010 to the present, adult patients with TRD or chronic PTSD, a PTSD or TRD diagnosis as determined by a cutoff score on a validated measure, MDMA-assisted psychotherapy, and ketamine-assisted psychotherapy. Exclusion criteria were defined as: articles published before 2010, articles not written in English, patients under 18 years of age, patients with acute PTSD, and PTSD or TRD diagnoses not determined by a cutoff score on a validated measure. Although studies that included primary or secondary outcomes measured using the Clinician-Administered PTSD Scale (CAPS) scoring were preferred, it did not warrant article exclusion as this criterion would substantially limit the number of articles available for appraisal. A total of 8 studies met the described inclusion criteria and were selected for this SR. A PRISMA flow diagram in Figure 1 demonstrates a visual outline of this process.[14]

Table 1. Inclusion and Exclusion Criteria

Inclusion	Exclusion
Population: • Adults (> 18 years old) • Patients with TRD or chronic PTSD Diagnosis:	Population: • Children (<18 years old) • Patients suffering from acute PTSD • Patients suffering from acute depression • Patients who were pregnant

• A PTSD or TRD diagnosis as determined by a cutoff score on a validated measure Intervention: • Studies on MDMA-assisted psychotherapy in reducing the experience of PTSD or TRD • Ketamine-assisted psychotherapy in reducing the experience of PTSD or TRD Primary or Secondary Outcomes: • MDMA-assisted psychotherapy studies that report a reduction in the experience of PTSD or TRD • MDMA-assisted psychotherapy studies that report no change in the experience of PTSD or TRD • Ketamine-assisted psychotherapy studies that report a decrease in the experience of PTSD or TRD • Ketamine-assisted psychotherapy studies that report no change in the experience of PTSD or TRD Type of Study: • English language • Randomized Controlled Trials (RCTs) • Case Studies • Systematic Reviews • Publication 2010- Present	• Patient with concomitant comorbidities in which MDMA/Ketamine therapy would exacerbate (ex: CAD) • Patients with substance abuse/dependence Diagnosis: • PTSD or TRD diagnoses not determined by a cutoff score on a validated measure Intervention: • Studies on MDMA-assisted psychotherapy in reducing the experience of anything other than PTSD or TRD Primary Outcomes: • Anything other than PTSD or TRD Type of Study: • Non-English • Questionnaire • Theses • Publication before 2010

Figure 1. PRISMA Flow Diagram



RESULTS OF LITERATURE REVIEW

Study Selection

In their totality, the selected peer-reviewed studies included a vast population of patients possessing chronic, treatment-resistant PTSD or MDD. An exact number was not calculated, as RCTs, SRs, and retrospective cohort studies were all included, with Varker et al., an SR, failing to identify its patient total. With consideration of the studies that did determine their patient sums, it is known that the studies in combination surpassed an entirety of 484 patients.

Study Characteristics

All reports were published between the years 2013 to 2020 in the English language. The patient demographic characteristics did not vary significantly across all eight studies. Interventional characteristics, however, did differ. This variation is secondary to a lack of standardization around the clinical use of MDMA and the attempt to discover the most successful way to administer it.

Definitions and Outcomes

To evaluate for PTSD symptom reduction, the primary measurement tool throughout the literature was CAPS scoring. This method is a DSM-IV-based, structured interview designed to quantify symptoms of PTSD.[3] Criteria for PTSD are defined by a CAPS score of $\geq$ 50, in addition to having PTSD for at least six months.[3,7,9,15,17]

The mean age of all eight studies was between 36.4 to 52.1 years. Beyond their psychological disorders, participants were regarded as healthy and lacked severe comorbid cardiac, respiratory, and metabolic conditions that would put them at risk during Ketamine or MDMA administration. By association and in conjunction with anesthesia considerations, this could be defined by the American Society of Anesthesia (ASA) classification system as ASA ones and twos. Additionally, studies required patients who admitted to previous substance abuse or dependence to be abstemious for a defined period before enrollment in the study.

Risk of Bias

The Cochrane Handbook Collaboration's Risk of Bias tool was utilized to assess the risk of bias in all studies.[20] A low bias risk was maintained secondary to the randomized allocation of patients among experimental groups, those receiving MDMA doses, and the control group, those receiving placebo doses. Randomization was accomplished through web-based systems, as in Mithoefer et al[7] and Ot'alora et al[15]. The risk of bias in Murrough et al[19] parallels this by articulating its randomization scheme generated using permuted block randomization of size six. Although double-blind randomization was carried out in Oehen et al[3], performance bias was difficult to ascertain within this study. Specifically, there is a failure to distinguish how individual assignments between groups were concealed from investigators.

In Feder et al[17], the randomized allocation of patients between experimental and control groups maintained the double-blind. Bias risk remained low throughout the study because only the research pharmacy was aware of the drug identity. Other individuals, such as the anesthesiologists, patients, and data analysts, were blinded to randomization order.[17]

In the retrospective study by Hartberg et al.,[16] there is a moderate risk of bias. Although records were concealed and standardization of therapy design was followed, a risk of reporting bias exists inherent to the fact that the clinical setting was a private, suburban psychiatric practice with clinicians who had been previously utilizing Ketamine as augmentation therapy for over three years.[16] Comparatively, the SR by Li et al[18] demonstrates a low risk of bias as each study addressed randomization and maintenance of concealment, though specific modalities were not discussed at length.

The risk of attrition bias cannot be overlooked, as many studies spanned over several years. Specifically, Feder et al[17], Ot'alora et al[15], and Oehen et al[3] had participants withdraw from their trials. Feder and Oehen disclose why, credited to adverse effects from MDMA or Ketamine infusions, one participant found a job, one failed to follow up, one was removed due to delayed-onset sedation, and one was removed due to low baseline PTSD symptoms.[15,17] Alternatively, Oehen et al[3] fail to acknowledge the rationale behind one of their participant's discontinuations.

DISCUSSION OF THE LITERATURE REVIEW

Summary of Evidence

Three RCTs were appraised that formatted their study into experimental cohorts receiving active doses of MDMA and control cohorts receiving inactive, placebo doses. Active dosages were defined as 100 or 125 milligrams (mg) by Ot'alora et al[15], 75 mg to 125 mg by Mithoefer et al[7], and 125 mg followed by 62.5 mg supplementation doses two and a half hours later by Oehen et al.[15] Inactive dosing was identified as 40 mg, 0 to 40mg, and 25 mg, followed two and a half hours later by 12.5 mg, respectively.[3,7,15]

All RCTs were consistent in reporting that therapeutic doses of MDMA in conjunction with psychotherapy generated more significant decreases in CAPS scoring compared to the control.[3,7,15] Oehen et al, however, did not deem the overall reductions as statistically significant ($p = 0.066$) at the defined initial endpoints of the study (baseline, three weeks after the second and third MDMA infusion, and at the 2-month and 1-year follow-up).[3] Statically and clinically significant self-reported improvement was only described according to the Posttraumatic Diagnostic Scale (PDS) ($p = 0.014$).[3] The Oehen et al study waivers from the previously discussed methodologies by proposing supplemental dosing to all participants in both study groups. Specifically, the active, full-dose group received 125 mg of MDMA followed two and a half hours later by 62.5 mg, whereas the active placebo group was dosed initially with 25 mg followed by 12.5 mg in the same time frame.[3]

With participants randomly assigned between experimental and control groups. Ot'alora et al[3] and Mithoefer et al[7] integrated MDMA dosing within eight-hour psychotherapy sessions. The blind was maintained in both studies until a third, primarily open-label session was carried out. The interpretation of the third psychotherapy session

results is limited, as the blind was broken, and a control group for comparison no longer existed. Oehen et al[3] broke the blind in their study as soon as the second therapy session ("stage 2") for individuals in the active placebo group.

Mithoefer et al[7] randomized a larger sample size of 103 patients. Seventy-two patients received active doses of MDMA (75-125 mg), and 31 patients received placebo or control doses (0-40 mg), all during eight-hour psychotherapy sessions. Consistent with the other MDMA-assisted RCTs, CAPS scores served to diagnose and measure changes in PTSD and depressive symptoms. This study was the longest in consideration, from 2004 to 2017, in various sites globally, from private practices to a psychiatric clinic.[7] After two psychotherapy sessions, 54.2% of the experimental group participants did not meet CAPS diagnostic criteria for PTSD compared to 22.6% in the control group.[7] The overall effect of treatment was rated according to between-group Cohen's *d* effect size, yielding a statistically significant value of 0.8.[7] Following a third psychotherapy session, symptom improvement continued to be more notable in the active dose group. PTSD diagnoses in the Ot'alora et al[15] study was significantly reduced in the group receiving 125 mg, with a mean variation from baseline CAPS scores to the one-month endpoint of −26.3. Secondly was the 100 mg group with a mean shift of -24.4, followed by the 40 mg active placebo group with a -11.5 change.[15]

Two RCTs, an SR, and a retrospective cohort study were appraised to draw a comparison between the effects of Ketamine in the setting of treatment-resistant mood and anxiety spectrum disorders. Feder et al[17] and Murrough et al[19] followed similar procedures, organizing an experimental group of ketamine infusions and a control group of intravenous (IV) midazolam. Murrough et al[19] explicitly discussed the potential of

Ketamine in reducing suicidal ideations (SI), measured according to the Beck Scale for Suicidal Ideation (BSI). This RCT provides initial support regarding the safety and tolerability of Ketamine in the setting of patients presenting with SI and risk for suicidal behavior. Though the twenty-four-hour post-infusion BSI score alterations were not considered statistically significant, the experimental group did experience a noteworthy change occurring at hour 48 ($p= 0.047$) in comparison to the control group.[19]

A retrospective study of 37 patients by Hartberg et al[16] conveys similar effectiveness in Ketamine's ability to reduce the number and duration of psychiatric hospital admissions by comparing the total of before and after ketamine intervention. The results portrayed a 70% reduction in hospital days and a 5% reduction in hospital admissions.[16] These cumulative findings establish a basis for future, well-powered studies concerning the efficacy of Ketamine in patients with mood disorders such as PTSD.

Feder et al[17] developed a proof-of-concept RCT establishing clinically significant CAPS scoring measures in patients who responded more to NMDA receptor modulation than midazolam. This trial provided the first randomized, controlled evidence that Ketamine can lead to a rapid clinical reduction of PTSD symptoms in chronic PTSD scenarios.[17] A mean difference in Impact of Event Scale-Revised (IES-R) scores outlined the primary outcomes of this study, with a more substantial decline in the ketamine cohort than midazolam (mean difference, 12.7 [95% CI, 2.5-22.8]; $P = .02$).[17]

Li et al[18] organized an SR analyzing six RCTs and one evidence-based guideline, investigating the clinical effectiveness, cost-effectiveness, and procedures for IV ketamine in treating adult patients with TRD and PTSD. In summary, three RCTs reported IV ketamine proved more effective than placebo (Fava et al) or midazolam

(Chen et al and Phillips et al) in remedying TRD.[18] On the contrary, the evidence-based guideline reported a strong recommendation against treating PTSD with Ketamine. This statement was made under the declaration of ketamine use as a monotherapy, supporting a greater efficacy in the setting of psychotherapy.[18]

Varker et al[9] organized an SR examining the value of the psychoactive drugs ketamine, MDMA, lysergic acid diethylamide (LSD), and psilocybin in treating PTSD. The study grew to predominately compare Ketamine and MDMA as trials on LSD or psilocybin failed to be identified. The findings of the SR denounced any value to Ketamine as a standalone treatment in reducing CAPS scores, with a remission rate of PTSD symptoms of 80%.[9] In a direct comparison of ketamine-assisted psychotherapy to MDMA-assisted psychotherapy, the evidence for MDMA was superior (defined as "moderate") to the evidence associated with Ketamine (defined as "low").[9]

Recommendations for Future Research

Recommendations for future research include establishing an optimal dose of MDMA in the clinical setting. However, all three RCTs on MDMA-assisted psychotherapy administered at least 100 mg doses in their experimental groups.[3,7,15] The effects of one-time dosing versus continued supplemental dosing have also not been explored by these studies. In addition to lacking a defined optimal dose or optimal dosing regimen, all studies indicated a need for more well-powered studies to generate further evidence.

CONCLUSION OF LITERATURE REVIEW

Based on the literature review, there was sufficient evidence to suggest that using MDMA during psychotherapy sessions could limit the incidence of PTSD and reduce its associative symptoms of depression.[3,7,9,15] Comparison to Ketamine served to solidify the existing evidence supporting MDMA usage. Despite varying conclusions on Ketamine's efficacy in

patients with mental health disorders, it is still a more accepted treatment modality utilized in practice.

METHODOLOGY OF QUALITY IMPROVEMENT

Setting

The setting for this project was a 672-bed hospital in Miami Beach, Florida. Mount Sinai Medical Center (MSMC) is an independent, non-profit teaching hospital in Miami-Dade County. There is a significant elderly population in this county, with 22% over the age of 60.[20] Miami Beach Anesthesiology Associates (MBAA) provides anesthesia services in 12 operating rooms, an eight-bed gastrointestinal (GI) suite, a catheterization lab, in addition to multiple other areas on campus.

Recruitment

Before the recruitment of this learning module's participants, approval was obtained by the investigators from Florida International University (FIU) and MBAA at MSMC. Certified registered nurse anesthetists (CRNAs) and anesthesiologists made up the population of interest. MBAA provided a contact list inclusive of the target group, and recruitment was carried out virtually utilizing e-mail.

Project Participants

Eligibility was defined as full-time and part-time CRNAs employed by MBAA and working at MSMC. A total of 20 anesthesia providers were invited to pursue this learning module. Participation of student registered nurse anesthetists (SRNAs) was excluded from this project.

Intervention

This evidence-based education module was executed in stages. The intervention consists of a recruitment phase, a pre-test, an educational intervention, and finally, a post-test. Pretesting is administered to obtain a baseline of the participant's understanding of MDMA and the current inefficiencies of PTSD management in the clinical setting. Following the pre-test, subjects

listened to an evidence-based voiceover PowerPoint education module that identifies the need for improved PTSD treatment, states the occurrence of lifetime PTSD in North American adults, and identifies factors that have prevented MDMA as a viable clinical adjuvant. The module also defines and contrasts MDMA from Ecstasy, describes previous clinical effects associated with MDMA, and identifies the potential for future MDMA use in the clinical setting. The educational content is supported by the literature review and is referenced accordingly. Participants will take a post-test to determine learning module efficacy, knowledge growth, and overall subject matter interest following the learning intervention.

Procedures

Participation was instigated through an e-mail list of providers supplied by MBAA. Enclosed in the e-mail was an anonymous link to a pre-intervention questionnaire using the Qualtrics survey platform. The educational module was provided virtually and made available to subjects through e-mail. After completing the learning module, post-testing was carried out in the same fashion utilizing the Qualtrics survey platform. No personal or identifiable information was sought after or acquired throughout testing. The only item needed by the learner was either a computer or cell phone.

Protection of Human Subjects

As this is an educational intervention, there is no to minimal risk to participants. Risks were outlined in the consent (see Appendix B). Anonymity was ensured under the Qualtrics survey platform, and the investigator obtained no personal factors that could identify the subjects. Additionally, Institutional Review Board (IRB) approval was gained before any intervention was carried out (see Appendix C). All anonymous results were maintained on a password-protected computer.

Measurement

The data was exported from Qualtrics to the Statistical Package for the Social Sciences (SPSS), and an analysis was conducted. Descriptive statistics were utilized on pre and post-test

data sets to examine survey responses. A paired t-test was then performed, inspecting the significance of changes in knowledge and attitudes of anesthesia providers secondary to the educational intervention.

Analysis

The co-investigator DNP student will extrapolate statistically significant data from SPSS, utilizing this to establish patterns of change from participants. Growth or decline in knowledge from pre-test to post-test will be compared using random identification numbers (ID) allocated by the Qualtrics platform to preserve anonymity. Each question will be assessed, and measurements will be taken to establish personal change, change amongst the group, and the overall effectiveness of the educational intervention. Data collected will remain on a password-protected computer.

RESULTS OF QUALITY IMPROVEMENT

Pre-test and Post-test Sample

The pre-test demographics are identified in Table 2., shown below.

Table 2. Pre-Intervention and Post-Intervention Participation Demographic Data

Demographics	N (%)
Total Participants	8 (100%)
Gender	
Male	3 (37.5%)
Female	5 (62.5%)
Age	
25 - 35 yr.	5 (62.5%)
36 - 45 yr.	1 (12.5%)
46 – 55 yr.	2 (25%)
55 – 66 yr.	0 (0%)
Ethnicity	
Hispanic	4 (50%)
Caucasian	0 (0%)
African American	2 (25%)

Asian	1 (12.5%)
Other	1 (12.5%)
Education	
Masters	0 (0%)
Doctorate	8 (100%)
Years of Practice	
0 – 2 yr.	4 (50%)
2 – 5 yr.	1 (12.5%)
5 – 10 yr.	1 (12.5%)
10 – 20 yr.	2 (25%)

Sixteen individuals initially started the pre-test survey, six of which failed to complete the post-test survey. Two CRNAs neglected to enter their random ID number to allow the project's co-investigator to assign pre and post-test scores to the right surveyor. Subsequently, their data was omitted during dissemination.

Eight anesthesia providers accurately followed the pre-test and post-test instructions, and their demographics are presented in Table 2. Most of the participants were female (n=5, 62.5%), instead of male (n=3, 37.5%). Most individuals were also amongst the 25 to 35 age group (n=5, 62.5%). The remaining participant's ages were as follows: 36 to 45 years old (n=1, 12.5%), 46 to 55 years old (n=2, 25%), and no individuals from the 55 to 66-year age group. Various ethnicities were also represented amongst the surveyor's: Hispanic (n=4, 50%), African American (n=1, 12.5%), Asian (n=1, 12.5%), and other (n=1, 12.5%). There were no participants who identified as Caucasian. All participants were CRNAs with Doctoral degrees (n=8, 100%). Finally, individuals were asked about their years of CRNA practice: 0 - 2 years (n=4, 50%), 2 - 5 years (n=1, 12.5%), 5 - 10 years (n = 1, 12.5%), 10 - 20 years (n=2, 25%).

Pre-test Identification of Knowledge of PTSD Sequelae and Efficiencies of Treatment Modalities

The pre-test consisted of nine questions that assessed participants' baseline knowledge on the topics being measured by the investigators. These topics included current first-line treatment modalities for PTSD, the overall efficacy of the first-line modality, lifetime effects and incidences of PTSD, MDMA's history, mechanism of action, and side effect profile, how MDMA differs from Ecstasy, and MDMA's current FDA standing on approval. Pre-test scores are subsequently organized in Table 3.

Regarding the first-line treatment for PTSD identified by the APA, only two participants (25%) identified this correctly as psychotherapies. One participant (12.5%) rightly answered the average response to this mode of therapy as averaging around 10 to 20 percent. Nearly all interviewees (n=7, 87.5%) were aware of the lifetime effects and comorbid conditions associated with PTSD. Additionally, the lifetime incidence of PTSD across North America was answered correctly by five participants (n= 62.5%) as 6 to 9 percent.

Pre-test Identification of Current Knowledge and Perspective of MDMA-Assisted Psychotherapies

A general knowledge deficit of MDMA's history was recognized, with no participants (n=0, 0%) accurately distinguishing that MDMA originated from a precursor to a hemostatic substance. An understanding of how MDMA and Ecstasy differ was mixed amongst the group. Three providers (37.5%) correctly identified that MDMA is an abbreviated version of a single chemical compound in Ecstasy. Another three participants (37.5%) believed MDMA lacked the psychedelic properties of Ecstasy, and 25% answered MDMA contains an additional amine group. Only 2 participants (25%) confirmed MDMA's mechanism of action as a disrupter of the reuptake transport protein SERT, and 3 participants (37.5%) rightly identified that nystagmus was not a commonly reported MDMA side effect. A preponderance of the group (n=5, 62.5%) was aware at baseline that MDMA-assisted psychotherapy for PTSD management has not yet been approved by the FDA nor been made widely available. Following item analysis in SPSS, the average score for the pre-test knowledge assessment was 3.5 (SD=0.53).

Post-Test Identification of Knowledge of PTSD Sequelae and Efficiencies of Current Treatment Modalities

Following the PowerPoint educational module voluntarily viewed by participants, all eight individuals were retested on the same questions to establish any growth in knowledge. Most notably, a 50% (n=4) gain in knowledge was observed regarding identifying psychotherapies as the first line for PTSD treatment. 62.5% (n=5) of the participants correctly answered the North American lifetime PTSD incidence range, with a 12.5% increase identified from pre-test analysis.

Pre-test and post-test scores remained consistent regarding PTSD's sequela and associative comorbid ailments, with seven participants answering rightly under both pre and post-test conditions (87.5%). In addition, only one participant correctly identified the 10 to 20 percent response rate in patients receiving pharmacotherapies for PTSD treatments. Resultantly, this demonstrated an unexpected lack of knowledge growth between pre and post-testing.

Post-Test Identification of Current Knowledge and Perspective of MDMA-Assisted Psychotherapies

A 62.5% growth in knowledge was seen between pre and post-testing regarding MDMA's origin as a hemostatic substance. Five participants were able to identify this correctly following the educational intervention. Additionally, most participants (n=5) could also discern MDMA as an abbreviated version of a single chemical compound within Ecstasy tablets, reflecting a 25% knowledge growth from pre- to post-testing regarding the difference between MDMA and Ecstasy.

Knowledge was also gained by participants regarding MDMA's mechanism of action. Out of all eight participants, seven (87.5%) understood MDMA to be a substance that renders its effects via the disruption of the reuptake transport protein, SERT. Similarly, seven individuals (87.5%) from only 3 (37.5%) who answered correctly during pre-testing became aware that nystagmus was not an expected side effect of MDMA. Most of the group, plus an additional participant who originally answered incorrectly on pre-testing (n=6, 75%), was aware that

MDMA-assisted psychotherapy for PTSD management has not yet been approved by the FDA nor been made widely available. Overall, the average score for the post-test knowledge following the education module was 6.25(SD=2.43).

Table 3. Difference in Pre- and Post-Test Responses (Knowledge of PTSD Sequelae and Efficiencies of Current Treatment Modalities)

CORRECT RESPONSES	PRE-TEST	POST-TEST	DIFFERENCE
ACCORDING TO THE AMERICAN PSYCHOLOGICAL APPLICATION'S (APA'S) 2017 CLINICAL PRACTICE GUIDELINES, THE FIRST-LINE TREATMENT FOR PTSD HAS BEEN IDENTIFIED AS: ***PSYCHOTHERAPIES***	*25%*	*75%*	*50%*
OF PATIENTS RECEIVING PHARMACOTHERAPY FOR PTSD TREATMENT, HOW MANY RESPOND TO THERAPIES? ***10 TO 20%***	*12.5%*	*12.5%*	*0%*
PTSD CONTRIBUTES TO REDUCED LIFE QUALITY AND THE DEVELOPMENT OF COMORBID CONDITIONS SUCH AS: ***ALL THE ABOVE (EMERGENCE DELIRIUM, DEPRESSION, HYPERTENSION, OBESITY)***	*87.5%*	*87.5%*	*0%*
THE LIFETIME INCIDENCE OF PTSD IN ADULT AGED SAMPLES IN THE UNITED STATES AND CANADA RANGES FROM: ***6 TO 9%***	*62.5%*	*75%*	*12.5%*

Table 4. Difference in Pre- and Post-Test Responses (Knowledge and Perspective of MDMA-Assisted Psychotherapies)

CORRECT RESPONSES	PRE-TEST	POST-TEST	DIFFERENCE
HOW DOES MDMA DIFFER FROM ECSTASY? ***MDMA IS AN ABBREVIATED VERSION OF A SINGLE CHEMICAL COMPOUND THAT IS A COMPONENT OF ECSTASY TABLETS***	*37.5%*	*62.5%*	*25%*
WHICH OF THE FOLLOWING IS CORRECT REGARDING THE PHARMACOLOGY OF MDMA? ***CAUSES DISRUPTION OF THE REUPTAKE TRANSPORT PROTEIN SERT***	*25%*	*87.5%*	*62.5%*
MDMA-ASSISTED THERAPY FOR PTSD HAS: ***NOT YET BEEN APPROVED BY THE FDA***			

AND HAS NOT BEEN MADE WIDELY AVAILABLE	*62.5%*	*75%*	*12.5%*
ALL OF THE FOLLOWING ARE COMMONLY REPORTED SIDE EFFECTS OF MDMA PSYCHOTHERAPY EXCEPT: ***NYSTAGMUS***	*37.5%*	*87.5%*	*50%*
3-4 METHYLENEDIOXYMETHAMPHETAMINE (MDMA) WAS ORIGINALLY DEVELOPED WITH WHAT PHARMACOLOGIC INTENTION: ***PRECURSOR TO A HEMOSTATIC SUBSTANCE***	*0%*	*62.5%*	*62.5%*

Table 5. Difference in Pre- and Post-Test (Interest in MDMA use in clinical setting)

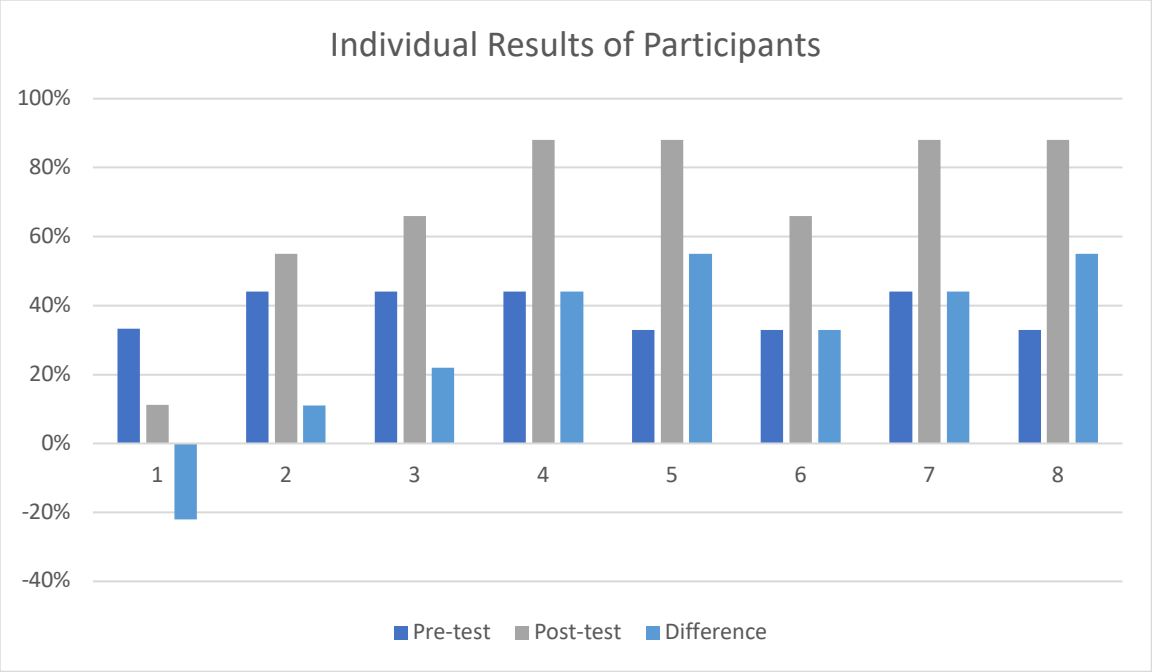
HOW LIKELY ARE YOU TO INVESTIGATE THIS NOVEL TREATMENT MODALITY ON YOUR OWN?	**PRE-TEST**	**POST-TEST**	**DIFFERENCE**
MOST LIKELY	*25%*	*25%*	*0%*
SOMEWHAT LIKELY	*25%*	*25%*	*0%*
SOMEWHAT UNLIKELY	*50%*	*50%*	*0%*
MOST UNLIKELY	*0%*	*0%*	*0%*

Table 5 depicts changes in the CRNA's perspective regarding the use of MDMA in the clinical setting. Overall, scores did not vary. Participants maintained the same level of interest or disinterest in the topic before and after the educational intervention.

DISCUSSION OF QUALITY IMPROVEMENT

Summary of Data

The results demonstrate an overall gain in knowledge between pre and post-testing, with only one participant with a lower post-test from pre-test score.



The average pre-test score of all participants was a 38.9%. Compared to the average post-test score of 69.5%, a 30.6% increase in knowledge was realized. The average improvement between individual pre-and post-testing was 30.3%. Only one (n=1, 12.5%) out of the eight participants showed a decline in knowledge following the education provided. The remaining seven anesthesia providers (n=7, 87.5%) increased their understanding of PTSD and MDMA.

Table 6. Paired T-test

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	PostOverall - PreOverall	2.75000	2.37547	.83986	.76406	4.73594	3.274	7	.014

Following data extrapolation from SPSS and according to the paired T-test, the mean change was 2.75, indicating that the average knowledge increase was 2.75 points higher on the post-test when compared to the pre-test. The results show a P value of 0.014, which is well below the statistically significant indicator of 0.05. The paired T-test demonstrates a statically significant knowledge base increase from the pre-test to the post-test due to the education module provided to participants.

Limitations

Limitations of this study include a small sample size that was not gender or age balanced. The bulk of participants were females (n=5, 62.5%) aged 25 to 35 (n=5, 62.5%). An increase in sample size would more accurately reflect the population of interest and improve the reliability of the study. Innate to qualitative research and secondary to the vastness of the topics of interest, PTSD and MDMA utilization, questions of improved quality and less subjectivity may have also altered pre-and post-testing scores.

As this project was volunteer-based, there is an inherent risk of self-selection bias. Though the investigators strived for concise instructions on the survey link, six participants who completed the pre-test failed to finish the post-test. Further, two individuals who finished their pre-and post-testing neglected to enter their ID number as instructed. The delivery method of an online study may have also limited the results.

Future Implications for Advanced Nursing Practice

The use of MDMA in a clinical setting has been proven safe and effective throughout multiple RCTs. Still, additional evaluation is required before MDMA can be taken seriously as a potential treatment modality. The outcomes of this study are essential in determining effective strategies to educate CRNAs on the need for enhanced treatments for PTSD and its associative symptoms of depression and the current data on the utilization of MDMA in practice. According to the information collected, the educational intervention successfully improved anesthesia provider knowledge of the sequelae of PTSD, inefficiencies of current PTSD treatment modalities, and MDMA as a clinical adjuvant. The results of this study can be applied to a broader population to develop a greater understanding of a clinician's willingness to investigate and approach MDMA administration. Coupled with evidence generated from the systematic review, the results of this study could drive future extension of MDMA-assisted psychotherapy into phase three trials and ultimately as a potential anesthetic option.

Conclusions

As denoted throughout the research, individuals with PTSD and accompanying MDD represent a subpopulation prone to a sequela of other comorbid conditions. This puts these patients in an increased need for both medical and surgical services. There is an undeniable need for more research to improve patient treatment options. An area of vulnerability for these patients is the perioperative period, where a standard of care is lacking. As supported by the SR, these individuals are more likely to experience ED, yielding unintentionally prolonged hospital stays and increased morbidity and mortality.

MDMA's use as an adjuvant to therapy has been and continues to be explored. MDMA's psychedelic and dissociative properties are somewhat comparable to Ketamine, an IV anesthetic grossly accepted by the clinical community. The outcomes of this study assist in gauging the CRNA's willingness to approach novel treatment modalities in the face of specialty populations who need it most. More specifically, patients who have PTSD have widely benefitted from MDMA-assisted psychotherapy throughout copious RCTs and phase 2 trials.

Though providers' attitudes regarding MDMA as a clinical adjuvant did not change secondary to the learning module, there was some interest at baseline. A statically significant knowledge base increase was shown following the intervention, proving the PowerPoint a valuable tool in expanding CRNA's learning. Though there remains a long way to go, there is a potential future for MDMA's use in the clinical setting.

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Appendix A

Miami Beach Anesthesiology Associates, Inc.

Mount Sinai Medical Center • Division of Anesthesia

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Jennifer Wright MD

J.P. Mato DNP, CRNA
CRNA Director &
F.I.U Coordinator
U.M. Coordinator
Barry Univ. Coordinator

Paula Schultz DNP, CRNA
OB-Chief CRNA

March 1, 2021

Yasmine Campbell, DNP, CRNA, APRN
Clinical Assistant Professor
Department of Nurse Anesthetist Practice
Florida International University

Dr. Campbell,

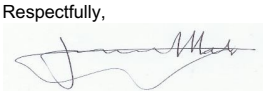
Thank you for inviting Mount Sinai Medical Center to participate in Doctor of Nursing Practice (DNP) project conducted by Brittany Williams entitled "An Evidence Based Learning Module Implementation to Expand CRNA Knowledge of Post-Traumatic Stress Disorder (PTSD) and the Use of 3,4-Methylenedioxymethamphetamine (MDMA) Assisted Psychotherapies in Patients who have PTSD and Other Alike Disorders" in the Nicole Wertheim College of Nursing and Health Sciences, Department of Nurse Anesthetist Practice at Florida International University. I have warranted her permission to conduct the project using our providers.

Evidence-based practice's primary aim is to yield the best outcomes for patients by selecting interventions supported by the evidence. This project intends to evaluate if a structured education targeting providers will increase knowledge on the care of patients who use MDMA-assisted psychotherapy for PTSD.

We understand that participation in the study is voluntary and carries no overt risk. All Anesthesiology providers are free to participate or withdraw from the study at any time. The educational intervention will be conveyed by a 15-minute virtual PowerPoint presentation, with a pretest and posttest questionnaire delivered by a URL link electronically via Qualtrics, an online survey product. Responses to pretest and posttest surveys are not linked to any participant. The collected information is reported as an aggregate, and there is no monetary compensation for participation. All collected material will be kept confidential, stored in a password encrypted digital cloud, and only be accessible to the investigators of this study: Brittany Williams and Dr. Campbell. We expect that Brittany Williams will not interfere with normal hospital performance, behaving in a professional manner and following standards of care.

Prior to the implementation of this Educational project the Florida International University Institutional Review Board will evaluate and approve the procedures to conduct this project. Once the Institutional Review Board's approval is achieved, this scholarly project's execution will occur over two weeks. We support the participation of our Anesthesiology providers in this project and look forward to working with you.

Respectfully,



Jampierre (J.P.) Mato, DNP, CRNA, APRN
Executive CRNA Director
SRNA Coordinator/Supervisor
Electronic Mail: Jampierre@bellsouth.net
Mobile Phone: 954-668-6080

Appendix B

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ADULT ONLINE CONSENT TO PARTICIPATE IN A RESEARCH STUDY

"A Learning Module in Post-Traumatic Stress Disorder (PTSD) and the Use of 3,4-Methylenedioxymethamphetamine (MDMA) Assisted Psychotherapies in Patients who have PTSD and Other Alike Disorders

SUMMARY INFORMATION

Things you should know about this study:

- **Purpose:** This project aims to increase the provider's understanding of 3,4-Methylenedioxymethamphetamine (MDMA)-assisted psychotherapy in the setting of Post-Traumatic Stress Disorder (PTSD).
- **Procedures**: If you choose to participate, you will be asked to complete an e-mailed pre-test/post-test and watch a virtual educational voiceover PowerPoint.
- **Duration:** This will take about 20 minutes of your time
- **Risks**: There will be minimal risks involved with this project, as would be expected in any type of educational intervention, which may have included mild emotional stress or mild physical discomfort from sitting on a chair for an extended period of time, for instance.
- **Benefits:** The main benefit to you from this research is: Increase the knowledge of anesthesia providers on the use of MDMA as a source of psychotherapy and the anesthesia considerations of caring for patients who use these drugs for therapy
- **Alternatives:** There are no known alternatives available to you other than not taking part in this study.
- **Participation:** Taking part in this research project is voluntary.

Please carefully read the entire document before agreeing to participate.

PURPOSE OF THE PROJECT

You are being asked to be in a quality improvement project. The purpose of this project is to increase the provider's understanding of 3,4-Methylenedioxymethamphetamine (MDMA)-assisted psychotherapy in the setting of Post-Traumatic Stress Disorder (PTSD).

NUMBER OF STUDY PARTICIPANTS

If you decide to be in this study, you will be one of 20 people in this research study.

DURATION OF THE PROJECT

Your participation will require about 20 minutes of your time.

PROCEDURES

If you agree to be in the project, we will ask you to do the following things:

- Complete an online 10 question pre-test survey via Qualtrics, an online survey product for which the URL link is provided

- Review the educational PowerPoint module lasting 10 minutes via Qualtrics and online survey for which the URL link is provided
- Complete the online 10 question post-test survey via Qualtrics, an online survey product for which the URL link is provided

RISKS AND/OR DISCOMFORTS
There will be minimal risks involved with this project, as expected in any type of educational intervention, which may have included mild emotional stress or mild physical discomfort from sitting on a chair for an extended period of time.

BENEFITS
The following benefits may be associated with your participation in this project: Increase the knowledge of anesthesia providers on the use of MDMA as a source of psychotherapy and the anesthesia considerations of caring for patients who use these drugs for therapy. The overall objective of the program is to increase the quality of healthcare delivery, improve the health of our patients, and increase patient engagement.

ALTERNATIVES
There are no known alternatives available to you other than not taking part in this project. However, if you would like to receive the educational material given to the participants in this project, it will be provided to you at no cost.

CONFIDENTIALITY
The records of this project will be kept private and will be protected to the fullest extent provided by law. If we might publish any sort of report, we will not include any information that will make it possible to identify you as a participant. Records will be stored securely, and only the project team will have access to the records.

COMPENSATION & COSTS
There is no cost or payment to you for receiving the health education and/or participating in this project.

RIGHT TO DECLINE OR WITHDRAW
Your participation in this project is voluntary. You are free to participate in the project or withdraw your consent at any time during the project. Your withdrawal or lack of participation will not affect any benefits to which you are otherwise entitled. The investigator reserves the right to remove you without your consent at such a time that they feel it is in the best interest.

RESEARCHER CONTACT INFORMATION
If you have any questions about the purpose, procedures, or any other issues relating to this research project, you may contact Brittany Williams at 772-475-4254, bwill192@fiu.edu or Dr. Yasmine Campbell, 305-348-9894, ycampbel@fiu.edu.

IRB CONTACT INFORMATION
If you would like to talk with someone about your rights of being a subject in this project or about ethical issues with this project, you may contact the FIU Office of Research Integrity by phone at 305-348-2494 or by e-mail at ori@fiu.edu

PARTICIPANT AGREEMENT
I consent by participating in the survey. I have read the information in this consent form and agree to participate in this project.

Appendix C

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Office of Research Integrity
Research Compliance, MARC 414

MEMORANDUM

To: Dr. Yasmine Campbell
CC: Brittany Williams

From: Maria Melendez-Vargas, MIBA, IRB Coordinator 

Date: April 7, 2021

Protocol Title: "An Evidence Based Educational Module On Anesthesia Considerations On Patients With MDMA Assisted Psychotherapy In The Reduction of Post-Traumatic Stress Disorder Symptoms"

The Florida International University Office of Research Integrity has reviewed your research study for the use of human subjects and deemed it Exempt via the **Exempt Review** process.

IRB Protocol Exemption #: IRB-21-0137 **IRB Exemption Date:** 04/07/21
TOPAZ Reference #: 110225

As a requirement of IRB Exemption you are required to:

1) Submit an IRB Exempt Amendment Form for all proposed additions or changes in the procedures involving human subjects. All additions and changes must be reviewed and approved prior to implementation.
2) Promptly submit an IRB Exempt Event Report Form for every serious or unusual or unanticipated adverse event, problems with the rights or welfare of the human subjects, and/or deviations from the approved protocol.
3) Submit an IRB Exempt Project Completion Report Form when the study is finished or discontinued.

Special Conditions: N/A

For further information, you may visit the IRB website at http://research.fiu.edu/irb.

MMV/em

Appendix D

Nicole Wertheim College of Nursing and Health Sciences
Department of Nurse Anesthetist Practice

Uses of Immersive Virtual Reality Distraction as an adjunct to anesthesia to decrease levels of pain in patients experiencing acute procedural pain: An Evidence-Based Educational Module

Dear Mount Sinai Medical Anesthesia Department,

My name is Brittany Williams, and I am a student from the Anesthesiology Nursing Program Department of Nurse Anesthetist Practice at Florida International University. I am writing to invite you to participate in my quality improvement project. This project aims to improve health care provider knowledge regarding PTSD and the existing body of research of MDMA-assisted psychotherapies in patients suffering from this disorder and others alike.

You are eligible to participate in this project because you are a Mount Sinai Medical Anesthesia Department member.

If you decide to participate in this project, you will be asked to complete and sign a consent form for participation. Next, you will complete a pre-test questionnaire, which is expected to take approximately 5 minutes. You will then be asked to view an approximately 15-minute-long educational presentation online. After watching the video, you will be asked to complete the post-test questionnaire, which is expected to take approximately 5 minutes. *No compensation will be provided.*

Remember, this is completely voluntary. You can choose to be in the study or not. If you'd like to participate or have any questions about the study, please e-mail or contact me at bwill192@fiu.edu or 772-475-4254.

Thank you very much.

Sincerely,

Brittany Williams, SRNA, BSN, CCRN

Appendix E

The primary aim of this QI project is to expand the knowledge of CRNAs regarding PTSD and the existing body of research of MDMA-assisted psychotherapies in patients suffering from this disorder and others alike.

Please answer the question below to the best of your ability. The questions are in multiple-choice format and are meant to measure knowledge and perceptions of MDMA in the clinical setting.

By clicking the "next" button, you acknowledge that your participation in this study is voluntary, you are at least 18 years of age, and that you may choose to terminate your participation in the study at any time and for any reason.

Demographic Questions

- Gender:
  - Male
  - Female
  - Other
- Age:
  - _____

- Ethnicity:
  - Hispanic
  - Caucasian
  - African American
  - Asian
  - Other

- Position/title:
  - _____

- Level of Education:
  - Bachelors
  - Masters
  - Other _____

- How many years have you been an anesthesia provider?
  - 1-2 years

- 2-5 years
- 5-10 years
- > 10 years

Knowledge

According to the American Psychological Association's (APA's) 2017 clinical practice guidelines, the first-line treatment for PTSD has been identified as:

a. SSRI therapy
b. SNRI therapy
c. Long-term counseling
d. Psychotherapies

Of patient's receiving pharmacotherapy for PTSD treatment, how many respond to therapies?

a. 5 to 10%
b. 10 to 20%
c. 20 to 30%
d. 30 to 40%

3,4-Methylenedioxymethamphetamine (MDMA) was originally developed with what pharmacologic intention:

a. Appetite suppressant
b. Originated as a psychedelic used only recreationally
c. Precursor to a hemostatic substance
d. Analgesic

PTSD contributes to reduced life quality and the development of comorbid conditions such as:

a. Emergence delirium
b. Depression
c. Hypertension
d. Obesity
e. All the above

How does MDMA differ from Ecstasy?

a. MDMA is an abbreviated version of a single chemical compound that is a component of Ecstasy tablets
b. It doesn't, they are the same substance
c. MDMA contains an additional amine group
d. MDMA lacks the psychedelic properties of Ecstasy

The lifetime incidence of PTSD in adult aged samples in the United States and Canada ranges from?

a. 1 to 5 %
b. 6 to 9 %
c. 20 to 24 %
d. 45 to 51 %

Which of the following is CORRECT regarding the pharmacology of MDMA?

a. Causes disruption of the reuptake transport protein SERT.

b. Enhances GABA receptor modulation
c. Its administration increases the net release of monoamine neurotransmitters from axon terminals
d. It increases Na+ channel resting membrane potential

MDMA-assisted therapy for PTSD has:

a. Has not yet been approved by the FDA but has been made widely available
b. Has been approved by the FDA but has not been made widely available
c. Has not yet been approved by the FDA and has not been made widely available

All the following are commonly reported side effects of MDMA psychotherapy EXCEPT:

a. Nystagmus
b. Elevated blood pressure
c. Tachycardia
d. Anxiolysis

How likely are you to investigate this novel treatment modality on your own?

a. Most likely
b. Somewhat likely
c. Somewhat unlikely
d. Most unlikely

Appendix F

Evaluation Table 1

Citation and Theme of the article	Design/Method	Sample/Setting	Major Variables Studied and Their Definitions	Measurement And Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/Level
Oehen P, Traber R, Widmer V, Schnyder U. A randomized, controlled pilot study of MDMA (± 3,4-methylenedioxymethamphetamine)-assisted psychotherapy for treatment of resistant, chronic post-traumatic stress disorder (PTSD). *J Psychopharmacol*. 2013;27(1):40-52. doi: 10.1177/0269881112464827 Theme: Decreased CAPS-IV scores secondary to MDMA-assisted therapy; This RCT speaks specifically to the safety of MDMA in both therapeutic and	RCT; Pre/post CAPS score comparison of patients in an experimental group receiving 125 mg and 62.5mg, 2.5 hours later, of MDMA to a control group of patients receiving active placebo MDMA doses of 25 mg followed 2.5 hours later by 12.5 mg.	12 total participants. (10 females, 2 males, mean age 41.4 with previous inadequate response to PTSD treatment modalities). N=8 in the experimental group. N=4 in the control group. Drop out (n=1), who withdrew due to adverse effects after MDMA session 1. The study was conducted at non-disclosed clinical sites. The study was conducted in an outpatient setting, including one overnight stay after each MDMA session to assess safety.	IV1 = MDMA therapeutic dose administration vs. MDMA subtherapeutic dose administration. DVI= CAPS-IV scores at defined experimental endpoints. DV2= PTSD symptom severity measured by the Posttraumatic Diagnostic Scale (PDS)	CAPS-IV interview administered at baseline (T0), three weeks following second MDMA session (T1), three weeks after the third MDMA session (T2), two months (T3), six months (T4), and 12 months (T5) following the study's completion. The scale level is ratio because it is quantitative in nature. PDS scale was also used, a validated self-reporting means assessing PTSD symptom severity. The scale was level represents ratio data. Reliability is questionable as an unvalidated yet widely used German version of the PDS was used in the study.[3] CAPS and PDS scores were analyzed by nonparametric analysis of variance (ANOVA), using an F1-LD-F1 model.[3]	CAPS change scores by group for T0-T2: T0-T1: Active Placebo: -3.3 (9.9); Full dose: -3.4 (12.0). T1-T2: Active Placebo: 6.5 (10.3); Full dose: -12.2 (8.1) T0-T2: Active Placebo: -3.2 (15.3); Full dose: -15.6 (18.1). PDS change scores by the group for time T0-T2: Active Placebo: 7.3 (6.2); Full dose: -8.6 (13.0) Including T3-T5, in the experimental group, CAPS-IV scores decreased on average 15.6 points (23.5%), and PDS scores also reduced compared to an increase in the active placebo group;	The active placebo group showed an increase in average CAPS scores from T1 to T2, with a final average CAPS change score of -3.2 (15.3%); the Experimental group with full dose-subjects showed a decrease in CAPS scores by 15.6 points (23.5%); Change scores from T0-T2 in PDS averaged a 7.3 (6.2%) increase in placebo groups and a -8.6 (13.0%) change in the full-dose group.	The study ruled MDMA-assisted psychotherapy as a safe option when administered in a clinical setting. No serious, drug-related adverse outcomes were identified. Though statistically significant CAPS score changes were not realized, PDS self-reports rendered values that were both clinically and statistically significant (p = 0.014). Additionally, at 12-month follow-ups, CAPS scores continued to improve.	*Strength: RCT, level 1a evidence; Primary outcomes measured using the CAPS-IV (noted throughout the research to have good reliability and validity). *Limitations: Small sample size; inter-rater reliability/diagnostic adherence only assessed after the study. *Risk or harm: effects mild, well-tolerated. The study points out that the nature of this therapy (reexamining prior traumas) increases distress regardless of full dose vs. placebo psychotherapy and may warrant a need for intervention (i.e., medications or additional

subtherapeutic doses.				Both CAPS-IV and PDS scores were used to answer the research question. Safety was also assessed with vital sign measurement every half-hour for 4 hours following session termination.				psychotherapy) *Feasibility of use in practice: MDMA is not commercially available, and further research is indicated to verify the results.

Evaluation Table 2

Citation and Theme of the article	Design/Method	Sample/Setting	Major Variables Studied and Their Definitions	Measurement And Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/Level

Mithoefer MC, Feduccia AA, Jerome L, et al. MDMA-assisted psychotherapy for treatment of PTSD: Study design and rationale for phase 3 trials based on pooled analysis of six phase 2 randomized controlled trials. *Psychopharmacology (Berl)*. 2019;236(9): 2735-2745. doi: 10.1007/s00213-019-05249-5. Theme: Decreased CAPS-IV scores secondary to MDMA-assisted therapy	RCT; Pre/post CAPS score comparison of patients in an experimental group receiving actives MDMA doses (75, 100, or 125 mg) versus the control group who received an inactive placebo or low dose MDMA (0, 25, 30, or 40mg) both during 8-hour psychotherapy sessions.	One hundred three total patients, 44 males, and 61 females. Experimental group n=72. Control group n=31. Participants were primarily Caucasian aged 18 or older with a mean age of 40.5 with an inadequate response to previous PTSD treatments. Treatment occurred at six sites, USA (MP-1, MP-8, MP-12), Canada (MP-4), Switzerland (MP-2), and Israel (MP-9), five of which being private practices and one a psychiatric clinic. The study was structured with an overnight stay following an 8-h psychotherapy session.	IV1= MDMA active dose administration vs. MDMA placebo/control dose administration. DV1= CAPS-IV scores at defined experimental endpoints; DV 2= the post-psychotherapy measurement of depression via Beck Depression Inventory-II (BDI-II); DV3= Treatment-emergent adverse events (TEAEs)/ serious adverse events (SAEs) measured via self-reporting.	CAPS-IV interview administered during follow-up visits at 1 and 2 months following the second and third psychotherapy session. Scale level measurement was a ratio. The primary efficacy evaluation was made with a mixed-effect repeated measure model (MMRM) on change in CAPS-IV total score from baseline to post second and post third experimental session endpoints.[7] BDI-II self-reporting assessed symptoms of depression, and the data level was a ratio. Response reliability was concluded using a four-point Likert scale and summed to produce an overall score.[7] TEAEs/SAEs were measured via self-reporting, and the study concluded there was no unexpected MDMA-related side effect. The study did not identify a measurement scale. This level scale represents nominal data, and the reliability of self-reporting was not assessed.	Significant reduction of CAPS was distinguished from baseline to session #2 [t(95) = −4.25, P < 0.0001] between both the control and active groups. The most notable changes, however, were viewed within an estimated mean (SE) drop in scores between experimental and control cohorts (−30.4 (3.20) and − 10.5 (4.46) respectively); Ultimate findings can be summarized as 54.2% of participants in the experimental group not meeting PTSD diagnostic criteria compared to 22.6% of those in the placebo/control group.	The experimental group demonstrated significantly improved CAPS-IV score reductions from baseline compared to the control with an MMRM SE difference of − 22.0 (5.17), P < 0.001] between groups.[7]	The study of MDMA in the clinical setting of PTSD was deemed well-tolerated and efficacious in this trial's sample. Support was generated to expand MDMA-assisted psychotherapy into phase 3 trials.	*****Strengths: RCT, level 1a. Primary outcomes were measured with an independent rater using the CAPS-IV. Data were pooled across 6 phase 2 trials. Various therapy teams attained similar findings. The population was near gender-balanced. *Limitations**:** Interpretation of the 3rd experimental session is limited because it was an open-label for most participants and lacked a control variable. The sample size was mostly White/Caucasians. Slight variations in study design existed across all six trials. BDI-II was only carried out in four of the six studies. *Risk of harm is minimal provided inclusion and exclusion criteria, was followed for patient selection; potential for abuse, defined by the study as "low." *Feasibility is appropriate,

				Research questions were answered via pooling data from six phase 2 RCTs.				as proven by the results. However, the true measurement of feasibility relies upon expansion into phase 3 trials, which cannot happen because MDMA is not commercially available.

Evaluation Table 3

Citation and Theme of the article	Design/Method	Sample/Setting	Major Variables Studied and Their Definitions	Measurement And Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/Level
Ot'aola GM, Grigsby J, Poulter B, et al. 3,4-methylenedioxymethamphetamine-assisted psychotherapy for treatment of chronic post-traumatic stress disorder: A randomized phase 2 controlled trial. *J Psychopharmacol*. 2018;32(12): 1295-1307. doi: 10.1177/0269881118806297. Theme: Decreased CAPS-IV scores secondary to MDMA-assisted therapy	The RCT assesses the efficacy and the specific-dose response of MDMA-assisted psychotherapy via comparing pre and post-CAPS-IV scores in experimental groups (receiving active doses of 100 and 125 mg) to a low amount, control group (40 mg). Following the primary endpoint (1-months post 2nd blinded session), the blind was broken with an open-label session with all three previously defined groups receiving 100-125 mg active doses during integrative therapy sessions.	Twenty-eight patients (9 men, 19 women, mean age of 42.0, primarily Caucasian) failed to respond to at least one alternate PTSD treatment modalities. One participant withdrew from the 40 mg control group, and another from the 125 mg experimental group (though the study did not disclose why). MDMA was administered in therapy rooms of undisclosed locations.	IV1= MDMA therapeutic dose administration vs. MDMA subtherapeutic dose. DV1= post-psychotherapy CAPS-IV scores; DV2= Beck Depression Inventory-II (BDI-II); DV3= Pittsburgh Sleep Quality Index (PSQI) scores; DV4= Dissociative Experience Scale-II (DES-II) scores.	CAPS-IV, a ratio scale, with reliability in test-re-test method assessed using an analysis of variance (ANOVA) with α=0.05.[15] Secondary measure's reliability (BDI-II, PSQI, DES-II), all of which also being ratio scales, was assessed in the same way. Cohen's d independent-groups pretest-posttest design was used for comparator-subtracted effect size estimates.[15] Descriptive statistics were used to answer the research question by displaying the percentage of participants not meeting PTSD criteria on CAPS-IV compared to those attaining a $\geq$30% decrease in scores post-treatment.	Statistically significant reduction in CAPS-IV scoring from baseline to one-month s/p session 2 (defined as stage 1 of study). Active dose groups had the most significant declines (with mean changes of −26.3 (29.5) for 125 mg, -24.4 (24.2) for 100 mg, and −11.5 (21.2) for 40 mg.) Stage 2 of study (blind broken) though supportive of this SR's goal of rationalizing MDMA therapy in the setting of treatment-resistant PTSD) were then not considered by the author as breaking the blind reduced internal reliability. At 12-month follow-ups, CAPS-IV scores dropped	The active groups (MDMA doses 100 mg and 125 mg) had the largest reduction in total CAPS-IV scores at the primary endpoint (one-month post-study) with SD changes of −26.3 (29.5) for 125 mg, −24.4 (24.2) for 100 mg, and −11.5 (21.2) for 40 mg. PTSD symptoms persisted in being lower than baseline at 12-month follow-up ($p<0.001$), with 76% (n=25) not meeting PTSD diagnostic criteria. There were no TEAEs or SAEs.[15]	MDMA in the clinical setting of PTSD was deemed well-tolerated and efficacious in this trial's sample. Support was generated to expand MDMA-assisted psychotherapy into phase 3 trials.	*Strength: RCT, level 1a; Primary outcomes were measured with an independent rater using CAPS-IV. Pooled data across six phase 2 trials established reproducible findings. The sample size was near gender-balanced. *Limitations: Interpretation of the third experimental session is limited because it was an open-label for most participants and lacked a control group. The sample size consisted primarily of White/Caucasian. Slight variations in study design existed across all six trials (differences in timing of outcome measures, doses tested, number of blinded experimental sessions, & participant number in each dose

					approximately -9.6, with 76% of patients failing to meet PTSD diagnostic criteria.			group). BDI-II was only carried out in four of the six studies. *Risk of harm is minimal provided inclusion and exclusion, as defined by the study, were followed for patient selection; potential for abuse, though defined by the study as "low." *Feasibility of use is appropriate as proven by results; however, the true measurement of feasibility relies upon expansion into phase 3 trials; MDMA is not commercially available.

Evaluation Table 4

Citation and Theme of the article	Design/Method	Sample/Setting	Major Variables Studied and Their Definitions	Measurement And Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/Level
Hartberg J, Garrett-Walcott S, De Gioannis A. Impact of oral ketamine augmentation on hospital admissions in treatment-resistant depression and PTSD: A retrospective study. *Psychopharmacology (Berl)*. 2018;235(2): 393-398. doi: 10.1007/s00213-017-4786-3. Theme: Establishes ketamine's role in MDD/PTSD management, legitimizing its use as a comparison for this study.	A retrospective cohort study examined ketamine therapy on augmentation of hospital admission in patients suffering from TRD/PTSD.	The sample consisted of thirty-seven participants (28 females, nine males, > 18 years, no defined mean age). Participants were diagnosed with treatment-resistant MDD, 15 with a primary diagnosis of treatment-resistant PTSD. Treatment resistance was explicitly defined in the study, and patients were screened using the Kessler-10.[16] Retrospective analysis design accounts for a 0% attrition rate. The study reviewed the number and duration of admissions to a psychiatric hospital before and after ketamine therapy.	IV1= oral ketamine administration in the setting of treatment-resistant MDD and PTSD. DV1= inpatient hospital days in total. DV2= hospital admissions for each patient before vs. after ketamine therapy. DV3= BP readings recorded before and 30 min after ketamine administration.	Outcomes were measured using pairwise t-tests, which compared total inpatient hospital days and hospital admissions pre and post ketamine therapy. This data scale is an interval. The reliability of the study's retrospective, match pair analysis was not measured. Primary outcomes used to answer the research question included the number of days spent as an inpatient and the number of hospital admissions before and after treatment with Ketamine.	Of 37 patients identified, 171 total admissions to psychiatric facilities were recorded before oral ketamine treatment, 67 admissions of which credited to symptoms of PTSD. Amidst the study, 65 admissions were recorded ($p < 0.001$). After the study's completion, patients were only admitted to the hospital 23 times.	Inpatient hospitalization days were reduced by 70% in the ketamine group, and hospital admissions decreased by 65%.	Based on the results, the future of oral Ketamine in the clinical setting was identified as a promising pharmacologic adjunct; a stark comparison was made to IM/IV ketamine, declaring oral Ketamine as more approachable. Further investigation is both warranted and supported by this study.	*****Strengths include level 2a evidence with an extensive follow-up period (up to 3 years). There was also a clear comparison of outcomes between pre and post Ketamine treatment with matched-pair analysis. *Limitations included a matching period within the study that may introduce bias. No controls were named. *Risk of harm is limited with this method as it is a retrospective study. However, this design type may also fail to substantiate the findings. *****Feasibility of use is moderate since Ketamine is commercially available.

Evaluation Table 5

Citation and Theme of the article	Design/Method	Sample/Setting	Major Variables Studied and Their Definitions	Measurement And Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/Level
Feder A, Parides MK, Murrough JW, et al. Efficacy of intravenous ketamine for treatment of chronic post-traumatic stress disorder: A randomized clinical trial. *JAMA Psychiatry*. 2014;71(6):681-688. doi: 10.1001/jamapsychiatry.2014.62. Theme: Assists establishing ketamine's role in MDD/PTSD management, legitimizing its use as a comparison for our study; Supports a basis for further primary clinical studies on Ketamine.	RCT, comparing an experimental group receiving Ketamine to a control group receiving midazolam as an active placebo.	41 Total patients (aged 18-55.) N=22 in the experimental group with a mean age of 36.4. N=19 in the control group with a mean age of 35.7. A total of 4 participants withdrew after the 1st therapy session (one found a job, one failed to follow up, one was removed due to delayed-onset sedation, and one was removed due to low baseline PTSD symptoms). Thirty-one patients received 2nd infusion, with an additional 2 participants then withdrawing (one received higher than expected ketamine doses, and one felt uncomfortable during infusion therapy). Icahn School of Medicine conducted the study at Mount Sinai's Clinical Research Unit following an overnight fast.	IV1=IV ketamine (0.5 mg/kg) vs midazolam (0.045 mg/kg). DV1= PTSD symptom severity determined by Impact of Event Scale-Revised (IES-R); DV2= CAPS scores; DV3= Montgomery-Asberg Depression Rating Scale (MADRS); DV4= Quick Inventory of Depressive Symptomatology, Self-Report (QIDS-SR); DV5= Clinical Global Impression–Severity (CGI-S) and–Improvement (GCI-I) scales.	IES-R, a ratio scale, was used to measure primary outcomes. Secondary outcomes were measured using the ratio scales of CAPS-IV. MADRS, QIDS-SR, CGI-S, and CGI-I. A modified intent-to-treat analysis was used to answer the research question. An additional intention-to-treat analysis of covariance, adjusting for baseline IES-R score, was also conducted with all 41 patients using only first-period data to avoid bias and establish reliability.	ES-R scores 24-h post first infusions were meaningfully reduced in experimental compared to midazolam (mean difference of 12.7) PTSD symptoms of seven patients in the ketamine experimental group remained appreciably reduced at two weeks post-infusion therapy than in the control group.	More significant and rapid reductions in PTSD symptom severity were seen in the experimental group over the control at the 24-hour mark. MADRS and QIDS-SR scores at 24 hours did not yield significant results of experimental vs. control conditions. Analysis of CGI-S and CGI-I scores at 24 hours did yield data supporting experimental conditions over control. Mean CAPS score seven days after infusion did not differ significantly by treatment (the mean difference between groups being 8.7 [95% CI, −4.8 to 22.2]; P = .20)	Rapid reduction in PTSD symptom severity was established for the first time after ketamine infusions in chronic PTSD patients.	*Strengths include level 1a evidence. The control group uses an active placebo to strengthen the blind study (compared to a non-active placebo such as saline), shielding the primary outcome analyst from adverse effects occurring during the infusion day. *Limitations include that of 41 patients, only 35 completed the study. Many patients in the experimental group could correctly guess if they received Ketamine due to the higher rates of dissociative symptoms. This likely affected the integrity of the blind. *Risk of harm is moderate. Acute psychological adverse effects include perceptual disturbance, dissociative symptoms, and short-term cognitive impairment. Three patients

								required medical intervention due to elevated BP. *Feasibility of use is moderate. Access to Ketamine is reliant on the care center or hospital; If infusion doses are replicated, these findings are likely to be reproducible.

Evaluation Table 6

Citation and Theme of the article	Design/Method	Sample/Setting	Major Variables Studied and Their Definitions	Measurement And Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/Level
Li KX, Loshak H. *Intravenous ketamine for adults with treatment-resistant depression or post-traumatic stress disorder: A review of clinical effectiveness, cost-effectiveness and guidelines.* Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2019. http://www.ncbi.nlm.nih.gov/books/NBK551873/.	A systematic review of the evidence analyzing a total of six RCTs and one evidence-based guideline, examining the clinical effectiveness, cost-effectiveness, and procedures for IV ketamine in treating adult patients with TRD/ PTSD	Four primary studies were identified specific to the clinical efficacy of IV ketamine in patients with TRD in hospital settings. Sample sizes of RCTs ranged from 26 to 99 patients. The years of study varied, with publications occurring in 2017, 2018, and 2019.	IV1= Ketamine infusion. IV2= Midazolam; IV3= placebo. DV1= anti-suicidal effect measured by Hamilton Depression Rating Scale (HAMD), MADRS, or Columbia Suicide Severity Rating Scale (C-SSRS SI) scores. DV2= depression severity (measured with HAMD).	The quantitative ratio scales of HAMD, MADRS, and C-SSRS SI measured depression/SI reduction. The RCTs were assessed using the Downs and Black checklist.	**Chen**: An RCT concluding decreased suicidal effects measured by HAMD and MADRS in both the 0.5 mg/kg and 0.2 mg/kg IV single dose ketamine group compared with placebo. **Ionescu**: An RCT reporting six repeated, non-escalating IV doses of 0.5 mg/kg ketamine was not significantly different than placebo in patients for antidepressant or anti-suicidal efficacy. **Phillips**: A Crossover RCT showing decreases in depression severity (measured by MADRS total score) was statistically greater in the ketamine group than the midazolam group. 4-hrs post-infusion, the antidepressant response	Ketamine demonstrated more efficacy in reducing the severity of depression in patients with TRD and the severity of PTSD symptoms of patients with PTSD.[18]	"Three RCTs reported that IV Ketamine was significantly more effective than placebo and midazolam for the treatment of adults with TRD. One randomized controlled trial reported no significant difference between IV Ketamine (six repeated doses of 0.5 mg/kg) and placebo. One evidence-based guideline reported a strong recommendation based on low-quality evidence against treating PTSD with ketamine monotherapy. No relevant evidence regarding the clinical effectiveness of IV Ketamine for PTSD or the cost-effectiveness of IV Ketamine for TRD or	*Strength includes an RCT with level 1a evidence. *Limitations include a limited sample size. Studies also took place in varying countries with inconsistent populations. RCT's had varying follow-up periods that may have influenced results (ranging from 14 days to three months). Two studies used single-dose infusions of Ketamine instead of repeated IV dosing. CAPS scoring, the DSM-IV gold standard for PTSD diagnosing, was not used in this study. *Risk of harm was reported in 8.5% of patients, including headaches, vomiting, worsened depression, and SI. *Feasibility of use is moderate. The study did not outline specific guidelines regarding the

					rate was 27% in the ketamine group vs. 0% in the midazolam group. The remission rate was 5% in the Ketamine group vs. 0% in the midazolam group (not compared statically) **Fava:** An RCT showing depression severity (via HAM-D-6) was significantly lower in the 0.5 mg/kg and 1.0 mg/kg IV ketamine groups than placebo on days one and three post-infusion. For ketamine doses (0.1 mg/kg and 0.2 mg/kg), there was no significant difference between Ketamine and placebo in depression severity changes (via HAM-D-6).		PTSD was identified." [18]	use of Ketamine in TRD or PTSD patients. However, it did mention an indication for further primary clinical studies, which is the theme of this SR.

Evaluation Table 7

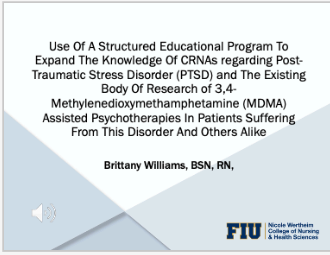
Citation and Theme of the article	Design/Method	Sample/Setting	Major Variables Studied and Their Definitions	Measurement And Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/Level
Varker T, Watson L, Gibson K, Forbes D, O'Donnell ML. Efficacy of psychoactive drugs for the treatment of post-traumatic stress disorder: A systematic review of MDMA, Ketamine, LSD and psilocybin. *J Psychoactive Drugs*. 2020:1-11. doi: 10.1080/02791072.2020.1817639. Theme: Establishes superiority of MDMA-assisted psychotherapy over ketamine monotherapy & assisted therapy.	An SR that examines the efficacy of MDMA, Ketamine, LSD, and psilocybin for the treatment of PTSD. RCTs and observational studies were eligible for inclusion. Ketamine monotherapy: Three RCTs were reviewed. Ketamine-assisted psychotherapy: Two RCTs examined Ketamine in combination with psychotherapy for PTSD. MDMA-assisted psychotherapy**:** Four RCTs were examining MDMA-AP for chronic PTSD.	The sample consisted of adult patients (> 18 years or older, mean age 52.1) diagnosed with PTSD or possessed a score from a validated measure indicating they had PTSD. Psychedelic therapy was administered in various outpatient settings, some trials requiring overnight stays after. Participant number varied by study.	IV1=Ketamine versus MDMA (as the SR failed to identify trials on LSD or psilocybin). DV1= CAPS scores determined at varying endpoints depending on the study under review; DV2= self-reported PTSD symptom improvement.	The persistence of PTSD or relapse was indicated by CAPS scores > 50. Studies were grouped and ranked using GRADE according to the type of drug used, \monotherapy or psychotherapy, and the post-treatment PTSD outcomes. The NHMRC checklist was used to assess bias and thus reliability.	Ketamine standalone showed initial improvements followed by high remission rates of 80%. Ketamine in assisted psychotherapy (TIMBER-K) vs. control of saline infusions (TIMBER-P) showed statistically similar CAPS reduction at 24-h post-infusion. Once TIMBER-P participants had relapsed PTSD symptoms, a cross-over design took place. The findings determined TIMBER-K experiences an increased duration of CAPS reductions (mean 24 days). MDMA in assisted psychotherapy had varied results. In	Ketamine as a standalone treatment modality proved low efficacy. Ketamine-assisted psychotherapy proved more effective than monotherapy, though less effective than MDMA-assisted psychotherapy. MDMA was not measured as a standalone treatment; MDMA-assisted psychotherapy proved the most effective in this SR.	The ranking of evidence of Ketamine as a standalone treatment was "very low" .[9] The ranking of evidence for Ketamine in combination psychotherapy was "low" .[9] The ranking of evidence for MDMA in combination psychotherapy was "moderate" .[9]	*****Strengths included level 1a evidence. *Limitations included a small trial number with methodological issues such as cross-over designs between experimental and control groups. *****Risk of harm was organized according to outcomes realized during each study. One acute increase in ventricular contractions occurred during an open-label session. *****Feasibility of use was moderate since Ketamine is commercially available, whereas MDMA is not.

					the first RCT, 10 out of 12 patients in the experimental group did not meet PTSD diagnostic criteria after MDMA infusion. In a smaller RCT, CAPS scoring was initially reduced in the experimental group, but scores did not differ drastically at the 3-week post-treatment. At 12 months, five participants were free of a PTSD diagnosis. In another RCT comparing MDMA active doses vs. low doses, the experimental group (active dose) had the greatest drop in CAPS scores. (Mean changes of −26.3 for 125 mg, −24.4 for 100 mg, and −11.5 for 40 mg.)[9]			

Evaluation Table 8

Citation and Theme of the article	Design/Method	Sample/Setting	Major Variables Studied and Their Definitions	Measurement And Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/Level
Murrough JW, Soleimani L, DeWilde KE, et al. Ketamine for rapid reduction of suicidal ideation: A randomized controlled trial. *Psychol Med*. 2015;45(16): 3571-3580. doi: 10.1017/S0033291715001506. Theme: Establishes a basis for future, well-powered studies concerning the efficacy of Ketamine in patients with mood disorders such as PTSD.	RCT; Participants with mood and anxiety spectrum disorders (such as MDD or PTSD) with clinically significant suicidal ideations (SI) were assigned to either an experimental group receiving (0.5mg/kg of IV ketamine) or an active placebo group (0.045mg/kg of IV midazolam).	Twenty-four total participants (16 female, eight males, mean age 42.4) Experimental group n=12. Control group n= 12. The setting was a single-site outpatient psychiatric clinic at the Icahn School of Medicine at Mount Sinai Institutional in NY between April 2012 and June 2014. No dropouts occurred during the study.	IV1= Ketamine versus Midazolam DV1= the Beck Scale for Suicidal Ideation (BSI) score; DV2= MADRS-SI score.	BSI, a ratio scale, measured SI at 24-h post-treatment. MADRS-SI, also a ratio scale, measured secondary outcomes at a 24-h post and beyond. Clinical significance was ascertained as a score of $\geq$4 on the MADRS-SI scale. Baseline participant characteristics, safety, and tolerability data were analyzed using descriptive statistics and t-tests or $\chi 2$ as appropriate.[19] These values were used to answer the research question	Interventions were well tolerated. 24-hr post-treatment, MADRS-SI score was significantly lower in ketamine group compared to midazolam group (1.8 ± 1.9 and 3.3 ± 1.6, respectively, $F1,21 = 4.3$, $p = 0.05$, Cohen's $d = 0.86$). The effect was not significant at 48 h (1.8 ± 1.9 and 3.2 ± 1.8, respectively, $F1,21 = 3.56$, $p = 0.077$, Cohen's $d = 0.77$), 72 h or seven days.	Twenty-four-hour post-infusion BSI scores changes were not statistically significant; The experimental group did experience. However, a noteworthy change occurred at hour 48 ($p= 0.047$) in comparison to the control group. This difference lost its significance at either the 72 hours or seven-day endpoint.[19]	The conclusions of this study provide initial support regarding the safety and tolerability of Ketamine in the setting of patients presenting with SI with clinically significant risk for suicidal behavior.	*Strengths include an RCT with level 1a evidence. *Limitations include a single-site design. The study could not demonstrate the effects of ketamine and midazolam after seven days. BSI baselines were obtained the same day as the study's initiation. *Risk of harm was limited as adverse effects that occurred were not considered to be related to study participation (i.e., hospitalization from worsening SI or depression). *Feasibility of use is moderate since Ketamine is commercially available.

Appendix G



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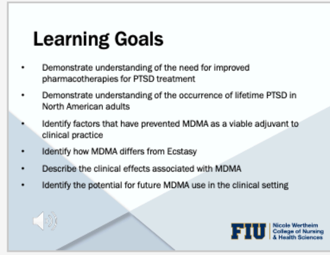

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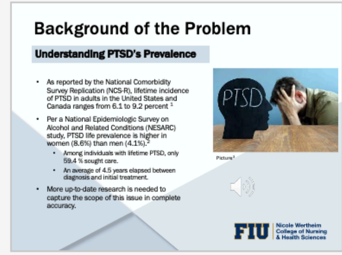

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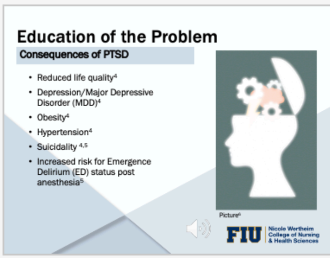

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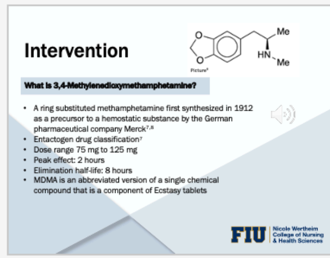

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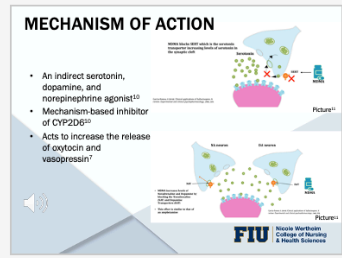

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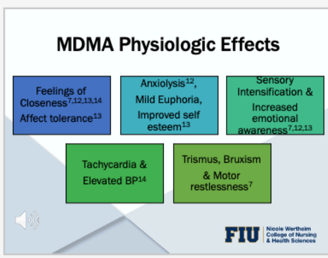

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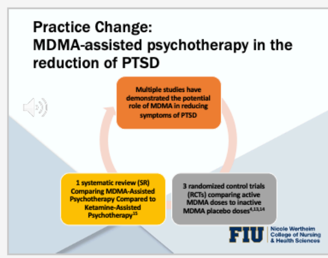

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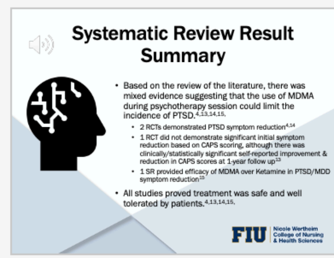

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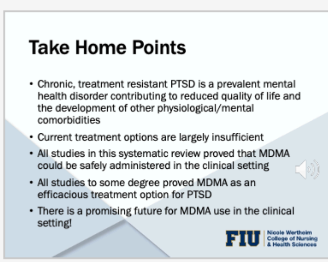

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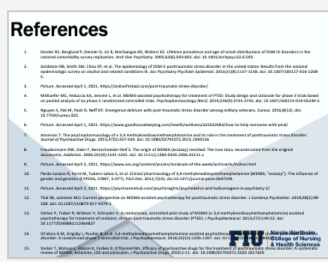

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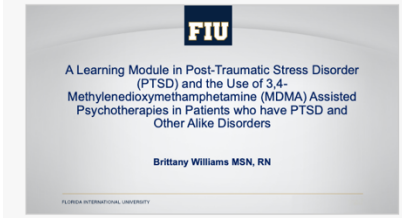
Appendix H



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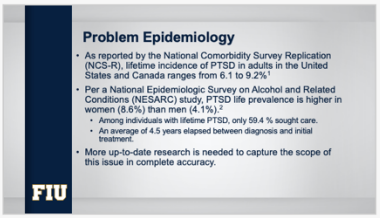

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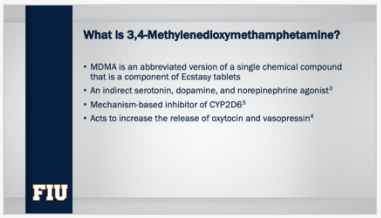

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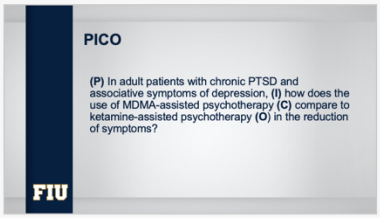

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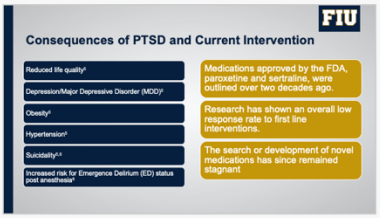

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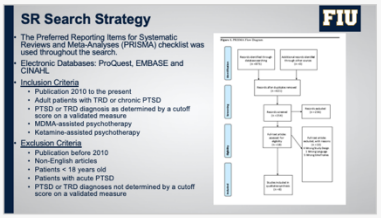

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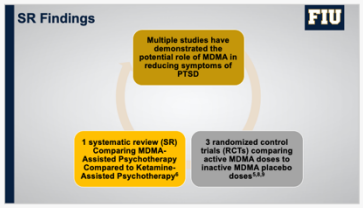

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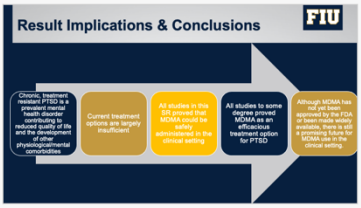

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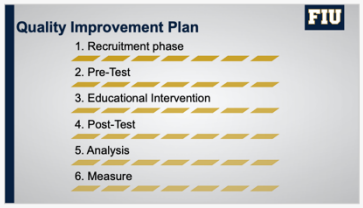

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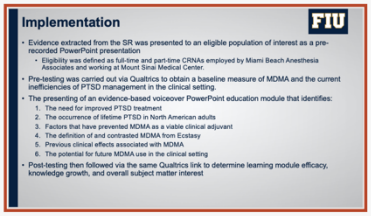

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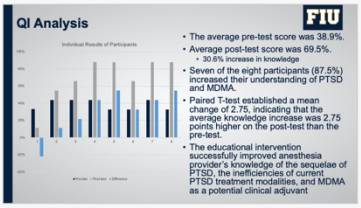

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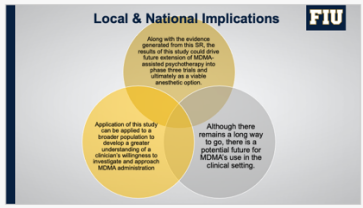

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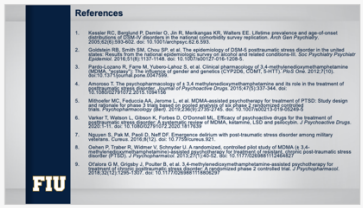

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