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Patient-Level Perspectives on the Use of Novel Psychotherapeutics for the Treatment of Substance Use Disorders by

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A thesis submitted to the faculty of the Medical University of South Carolina in partial fulfillment of the requirements for the degree of Master of Biomedical Science in the College of Graduate Studies.

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CHAPTER I
INTRODUCTION

Background and Need

Substance use disorders (SUDs) are a rapidly evolving public health crisis. SUDs are associated with a myriad of adverse consequences including overdose, contraction of infectious diseases, and development of psychiatric comorbidities such as depression (World Drug Report, 2020). While pharmacotherapies exist for certain SUDs, most current medications require daily adherence to self-administration, and long-term abstinence rate remain low (Mattick et al., 2001). Additionally, there are currently no FDA-approved medications to treat stimulant use disorders (such as cocaine, amphetamines), benzodiazepine use disorder and cannabis use disorder. Consequently, there is a clear need for novel, efficacious pharmacotherapies for treatment of SUDs.

Multiple prior studies including both randomized controlled trials and naturalistic studies suggest that medications known as psychedelics have potential therapeutic benefit in the treatment of addictions and other psychiatric disorders. In a dose-dependent manner, this class of compounds is associated with novel psychoactive experiences characterized by dream-like states, altered sensory perceptions, and an increased sense of universal connectedness. Psychedelic compounds are associated with a high safety profile with extremely low levels of morbidity and mortality, and limited evidence of any physical dependence (Johnson et al., 2018; Nichols, 2016).

Investigational study using these compounds for the treatment of mental health disorders has escalated in the past decade. Psilocybin and 3,4-Methylenedioxymethamphetamine (MDMA) have been particularly well studied, and in the past three years, the FDA granted “breakthrough therapy” designation to these medications for treatment resistant depression and post-traumatic stress disorder (PTSD), respectively. While these medications are considered somewhat controversial due to their unique psychoactive effects, a previous national level survey of the general population found that a majority of Americans supported research and potentially clinical

use of these medications for mental health disorders. Despite increasing evidence of efficacy in SUD treatment however, no prior study has investigated whether individuals with SUDs would be open to treatment with these new therapeutic agents. My hypothesis was that individuals with a SUD would demonstrate differential acceptance of these treatment modalities as a function of prior awareness of these medications.

Problem Statement

Although psychedelic medications appear efficacious in SUD treatment, no prior study has investigated whether individuals with SUDs would be open to treatment with this class of medications. Further, while prior clinical trials have been conducted using various psychedelics to treat patients with a SUD, individuals already involved in psychedelic therapy research may not display the same attitudes and opinions with SUD individuals who have not received these therapies.

Innovation

Collectively, the analyses provide critical insights into patient-perspectives on the use of these novel psychotherapeutics for the treatment of SUDs. This study had the advantage of utilizing previously completed nationwide survey data in a large population (N=920). Furthermore, this study provides essential information that will direct future research recruitment efforts and clinical considerations using these treatments and will inform future studies for this urgent public health need.

CHAPTER II
REVIEW OF THE LITERATURE

Substance use disorders (SUDs) are a rapidly evolving public health issue

SUDs affect an estimated 35.6 million individuals worldwide (World Drug Report, 2020). SUDs can lead to many adverse clinical consequences including contraction of infectious diseases,

overdose, and the development of comorbid psychiatric disorders (World Drug Report, 2020). SUDs are classified on a range from mild to moderate to severe, with severity being dependent on how many criteria are met according to the Diagnostic and Statistical Manual of Mental Disorders (DSM). Criteria include physiologic changes (i.e. craving, tolerance, and withdrawal symptoms), psychosocial problems (i.e. legal issues, occupational impairment, use in hazardous situations, decreased recreational enjoyment, family or social problems), and use despite harms to mental or physical well-being.

Addiction is generally characterized as a recurring cycle of binging/intoxication, withdrawal/negative affect, and preoccupation/anticipation also known as "craving" (Koob et al., 2016). This cycle worsens over time and involves changes in reward, stress, and executive function systems in the brain (Koob et al., 2016). Additionally, changes in brain activity associated with a mental illness, may increase an individual's risk to abuse substances by enhancing the drug's rewarding effects, reducing awareness of negative effects, and/or alleviating unpleasant symptoms of the mental disorder or the side effects of the medication used to treat it (NIDA, 2020).

When a drug of abuse is taken, origins and terminal areas of the ascending mesocorticostriatal dopamine systems are activated, largely contributing to the rewarding properties of these substances (Koob et al., 2016). When drugs of abuse are taken at doses producing intoxication, there is a fast and profound release of dopamine into the ventral striatum which binds and activates dopamine D1 receptors, producing the rewarding effects and triggering conditioned responses to the stimulus (Koob et al., 2016). Understanding changes at the molecular, cellular, and neurocircuitry levels that allow for the transition from an occasional substance user to a chronic substance user who suffers from loss of control in their drug intake is critical for the treatment of SUDs (Koob et al., 2016). Knowledge of relevant brain circuits, neurotransmitters, and neuromodulators has evolved substantially over the years and now include y-aminobutyric acid (GABA), glutamate, serotonin, acetylcholine, and endocannabinoid systems (Koob et al., 2016).

Substances of abuse work via neurotransmitter-specific neuroplasticity circuits in order to rewire executive function circuits, motivational circuits, and stress circuits resulting in poor inhibitory control and decision making (Koob et al., 2016). It is this rewiring that can lead to a once neutral stimuli now being associated with positive reward commonly referred to as reinforcement (Koob et al., 2016). When reinforcement occurs, it strengthens the rewiring of these neurotransmitter-specific reward circuits, making it much harder to stop using the drug and the motivation to binge again even greater. Furthermore, this repeated cycle of binging to intoxication and subsequent strengthening of reward circuits leads to the development of tolerance for the drug at the current dose being taken.

When tolerance occurs, a larger dose of the drug of abuse must be taken in order to achieve the same rewarding effects once felt previously, substantially increasing one's risk of overdose. Prior brain imaging studies have shown amphetamine/methylphenidate-induced striatal dopamine responses are 50% lower in detoxified users compared to an 80% lower response in active abusers (Koob et al., 2016). While experiencing drug tolerance, if the individual does not take a larger dose of the drug of abuse, they will begin to experience the withdrawal stage of addiction.

The withdrawal stage consists of several negative affects including increased stress, irritability, malaise, and even emotional pain (Koob et al., 2016). This is largely due to the recruitment of key brain stress systems such as corticotropin releasing factor (CRF), norepinephrine, and dynorphin to the amygdala (Koob et al., 2016). This decrease in reward and increase in stress function results in craving which drives the individual to compulsively seek out more of the drug, potentially engaging in risky activities to do so (Koob et al., 2016). These cravings are largely influenced by cues the individual has come to associate with the drug of abuse. Cues may vary widely from person to person, but can include a certain time of day, a particular room in the house, the sight of drug paraphernalia, etc. These cues that the individual has come to associate with the drug of abuse lead to a dopamine release in the striatum, amygdala, and prefrontal cortex

along with opioid peptide release in the anterior cingulate and frontal cortex (Koob et al., 2016), fueling the individual's craving.

Current therapies for SUDs are inadequate and novel treatments are needed

There are currently several medications for SUDs on the market today which have been granted FDA approval. These include pharmacotherapies for tobacco use disorder, alcohol use disorder and opioid use disorder. While these SUDs can be treated with medications, many existing pharmacotherapies require daily adherence to medication self-administration, and long-term abstinence rates remain low (Mattick et al., 2001). Additionally, individuals with co-occurring mental health disorders and substance use disorders report lower rates of treatment success, higher rates of psychiatric hospitalizations, and a higher prevalence of suicide (World Drug Report, 2020). It has been shown that only 18 % of addiction treatment programs and 9 % of mental health programs were able to provide pertinent treatment to dual diagnosis individuals in the United States (McGovern et al., 2014).

In the case of opioid use disorder, there are currently only 3 main FDA approved medications authorized for treatment, naltrexone, methadone, and buprenorphine - naloxone. Treatment with methadone may be used short-term in order to detoxify patients from opioids, however, it is also commonly used in long-term treatment provided the individual attends mandatory counseling due to the risks involved with methadone treatment (Butelman et al., 2017). Methadone can be fatal if taken in overdose and may also increase one's risk of severe liver disease with paired use of other substances such as alcohol or psychotropic medications like benzodiazepines and barbiturates (Kreek, Oratz, & Rothschild, 1978).

The opioid partial agonist medication, buprenorphine - naloxone, has a lower risk or overdose than methadone due to its ceiling effect on respiratory depression (Butelman et al., 2017). Drug counseling is highly recommended for treatment and patients must be seen at frequent

intervals until a stable dosage is achieved (Butelman et al., 2017). This can lead to a significant reduction in long term abstinence rates due to patient drop out. Additionally, current FDA approved medications to treat alcohol and tobacco use disorders require daily medication self-administration, sometimes multiple times a day, further contributing to low long-term abstinence rates for these SUDs. Moreover, there are currently no FDA-approved medications to treat stimulant use disorders (such as cocaine and amphetamines), benzodiazepine use disorder, or cannabis use disorder. Collectively, this demonstrates a substantial need for novel, efficacious pharmacotherapies for treatment of SUDs.

Novel psychoactive medications may improve ability to maintain abstinence across a broad variety of SUDs

A class of compounds with unique psychoactive effects called psychedelics, have shown early evidence of efficacy in the treatment of substance use disorders. In a dose dependent fashion, psychedelic compounds can temporarily produce dream-like states, altered sensory perceptions, and increased sense of universal connectedness. Unlike most existing SUD pharmacotherapies, these medications appear to improve ability to maintain abstinence across a wide spectrum of SUDs and may improve ability to maintain abstinence with only one or a few medication administrations (Curran et al., 2018). Evidence demonstrates that psychedelics have a high safety profile with extremely low levels of morbidity and mortality, and studies show limited evidence of any physical dependence (Johnson et al., 2018; Nichols, 2016). Psilocybin and 3,4-Methylenedioxymethamphetamine (MDMA) have been particularly well studied, and in the past three years, the FDA granted "breakthrough therapy" designation to these medications for treatment resistant depression and post-traumatic stress disorder (PTSD), respectively. Breakthrough therapy is granted when preliminary clinical data indicates that a drug intended to treat a serious medical condition has demonstrated substantial improvement over the currently available therapies (Commissioner, O., 2018).

Psilocybin is a naturally occurring psychedelic produced in a variety of mushrooms. Psilocybin broken down to its pharmacologically activated form, psilocin, in the gastrointestinal tract and kidneys (Psilocybin, 2016). Once converted to psilocin, it acts as a high-affinity agonist at several serotonin 5-HT receptors (Psilocybin, 2016). The most common of these being 5-HT2A receptors which are especially prominent in the prefrontal cortex, resulting in increased cortical activity (Psilocybin, 2016). Due to dysfunction in the monoamine systems of serotonin (5-HT) seen in SUDs (Bas et al. 2017), psilocin's action on the serotonergic pathway makes psilocybin a key drug of interest for the treatment of SUDs.

Psilocybin has demonstrated efficacy in the treatment of tobacco use disorder with 80% of participants showing seven-day point prevalence abstinence at 6th month follow-up (Johnson et al., 2014). A study on alcohol use disorder showed that participants reporting heavy drinking days 40% of the time at baseline were able to reduce heavy drinking days to <20% after just one or two treatment sessions (Bogenschutz et al., 2015). Furthermore, a study investigating treatment-resistant depression found that one week after 2 sessions, 71% of participants had >50% reduction in depression severity and 58% were completely in remission (Davis et al., 2020).

Ketamine is a racemic mixture of two enantiomers, esketamine (S-Ketamine) and arketamin (R-Ketamine) (Himmelseher et al. 2008). Ketamine first gained FDA approval in 1970 for its human use as an anesthetic (Jansen, 2000). Much research has gone into Ketamine since and it has shown great promise in the treatment of SUDs. A previous study demonstrated that after 3 treatments with ketamine combined with therapy, 50% of study participants were able to abstain from using heroin fully for over 1 year (Jones et al., 2018). In a related study with heavy alcohol users, it was discovered that nearly 2/3 of participants were able to maintain abstinence for over one year after a single session of ketamine in conjunction with psychotherapy (Jones et al., 2018). Furthermore, several other recent trials in cocaine users have shown that motivation to quit increases following a ketamine treatment. (Jones et al., 2018).

Additional studies have demonstrated an anti-depressant effect when participants were given sub-anesthetic doses of ketamine, leading to ultra-rapid remission of severe depression symptoms including thoughts of suicide (Jones et al., 2018). This anti-depressant effect is hypothesized to be mediated by ketamine's action as an NMDA receptor (NMDAR) antagonist (Strasburger et al., 2017). Antagonism of the NMDAR by Ketamine was hypothesized to increase overall activity in the prefrontal cortex due to NMDAR inhibition expressed on GABAergic interneurons (Zanos et al., 2018). This increase in activity produces various synaptic improvements including structural increase of spine densities at synaptic proteins, ultimately hypothesized to improve one's ability to learn new behaviors which may prove to be invaluable in the treatment of SUDs (Jones et al. 2018).

3,4-Methylenedioxymethamphetamine (MDMA) acts as an indirect serotonin agonist, acting on the serotonin transporter where it is then transported to the nerve terminal (Baker et al. 2004). Being inside the terminal affects the amount of serotonin which can be stored within vesicles and thus leads to a significant increase in serotonin release into the synapse (Baker et al. 2004). Additionally, MDMA increases release of dopamine and noradrenaline in what is believed to be a similar manner (Baker at al., 2004). In 2016, the FDA approved MDMA for phase 3 clinical trials as a treatment for post-traumatic stress disorder (PTSD), which is a condition that commonly occurs alongside addictions. A prior study from 2012 demonstrated that with 3 doses of MDMA administered under a psychiatrist's guidance, the patients reported a 56% decrease of severity of symptoms on average, and 66% no longer met the criteria for having PTSD by the end of the study with improvements lasting more than a year after therapy (Mithoefer et al., 2012).

Target population support for psychedelic treatments is unknown

Previous work has shown strong overall public support for research into this medication class (McCarriston, 2017). In a 2017 national survey of the general population, 53% of all respondents supported medical research into psychedelic drugs. A majority (63%) also said they

would personally be open to medical treatment with psilocybin, ketamine, or MDMA if they had a medical condition for which it was proven effective and safe (McCarriston, 2017). However, it is unknown whether individuals with SUDs have similar levels of support. A majority of individuals with SUDs will have tried more than one addictive substance, which suggests that they may have previously tried psychedelic compounds (McCance-Katz, 2019). However, SUDs are also characterized by avoidant thought processes however, and individuals often report using substances to cope with difficult feelings.

Given that psychedelic compounds can be associated with challenging psychoactive experiences, it is thus unclear whether individuals with SUDs will endorse a similar level of support to the general population, or whether they will endorse particular concerns about these prospective new treatment modalities.

CHAPTER III
METHODOLOGY

Research Design

A cross-sectional survey study was designed and administered in order to analyze patient-perspectives on the use of these novel psychotherapeutics for the treatment of SUDs. Prior to completion of the main survey, potential participants were required to first complete a pre-screener questionnaire. This questionnaire evaluated several criteria for SUDs in order to ensure that only those self-reporting criteria matching that of a SUD would be offered the opportunity to complete the full survey. IP constraints were set up to prevent participants from taking the survey more than once.

Recruitment

Recruitment was conducted primarily through advertisements placed on the internet (i.e. Craigslist). Both pre-screening and the survey were conducted using the secure web database,

REDCap. REDCap is primed to support online and offline data capture for research studies and operations.

Inclusion Criteria

To have been considered for inclusion in the study, participants must have been (1) over the age of 18, of any gender, race or ethnicity, (2) able to comprehend English, (3) able to provide informed consent and function at an intellectual level sufficient to allow accurate completion of the assessment instruments, (4) self-reporting at least 2 criteria for SUD, and (5) have used a substance of abuse at least once in the past month.

Exclusion Criteria

Potential participants were excluded if they (1) did not self-reporting at least 2 criteria for a SUD, (2) did not report using a substance of abuse at least once per month, (3) denied ever wanting to cut back on or stop using a substance of abuse, or (4) did not give their informed consent to participate in the study.

Screening and Informed Consent

Initial screening eligibility using the inclusion and exclusion criteria was conducted using a pre-screener questionnaire hosted via REDCap. Participants were informed that participation in the study was voluntary, and they could discontinue at any time. Participants were provided with an overview of the study procedures in advance.

Assessment Procedures

Following completion of informed consent, and provided that all inclusion and exclusion criteria were satisfied, eligible participants proceeded to take the "Opinions on Psychedelic Therapy" main survey. The survey took approximately 20 minutes to complete. The survey was anonymous, but participants were asked basic questions about themselves such as their age, gender,

race, and use of alcohol and various substances. Participants went on to answer questions regarding (1) their level of support for the psychotherapeutics psilocybin, ketamine and MDMA being used in medical trials, (2) whether or not they believe these psychotherapeutics could be a beneficial treatment for people suffering with addictions, and (3) whether or not they themselves would be willing to participate in one of these trials. The psychotherapeutics psilocybin, ketamine, and MDMA were specifically chosen to asses individual level of support as there have been multiple prior studies conducted which demonstrate their efficacy in the treatment of addictions and other psychiatric disorders and thus they would be most likely to continue to be used in future medical trials.

Participants were then asked to select from a list of 14 concerns regarding the use of psychedelics (psilocybin, ketamine, MDMA, or other psychedelic medications) to reduce or stop using alcohol or other drugs. The concerns listed were comprised of common fears that are associated with perceived possible consequences that might arise from taking a psychotherapeutic (fear of a bad trip, fear of losing one's mind, fear of job loss, etc.). Participants could select any number of concerns from this list or a "N/A" option if they had no concerns.

Participant Compensation

Participants were eligible to be compensated for their time with a $15 Amazon gift card. This gift card would be sent to their email address. If the participant did not wish to provide their email address, they may still take the survey, but they would not be able to receive compensation.

Data Analytic Procedure

All data from this survey was collected and managed using the secure REDCap (Research Electronic Data Capture) database. Furthermore, all data was analyzed using the SPSS statistical software platform. Baseline demographic characteristics were collected from all participants and descriptive statistics for the sample population were analyzed.

Research Questions and Hypotheses

AIM 1

To determine acceptance rates of the use of psychedelics as a therapeutic modality among individuals self-reporting SUDs. Based on previous studies which suggest that higher levels of education are associated with increased levels of acceptance of these new treatments in the general population, I hypothesized that prior knowledge of these treatment modalities would have the greatest impact on the level of support for these treatments. To test this hypothesis, we quantified the level of support for the use of psilocybin, ketamine, and MDMA as a function of prior knowledge of these psychedelic medications. Taken together, these data detail the role of how public awareness of these novel treatments modulates the support for their use in research and clinical contexts.

To test this hypothesis, the independent variable assessed was between prior psychedelic knowledge individuals and no prior psychedelic knowledge individuals. The dependent variable was characterized by the level of psychedelic support expressed between the two groups based on each individual's ranked choices regarding the use of psychedelics in medical research. This was accomplished through use of Mann-Whitney U.

AIM 2

To characterize concerns about the therapeutic use of psychedelics among individuals self-reporting SUDs. Given that these medications have unique psychoactive effects, I hypothesized that the number of concerns regarding the therapeutic use of psychedelics would be greatest in individuals who have never used psychedelics previously in contrast to those who had. We further explored whether prior use affects the type of concerns expressed. My prediction was that individuals not reporting prior use would be more likely to endorse concerns related to the

experience itself (i.e. fear of "going crazy") and that there would be no difference between groups on psychosocial concerns (i.e. fear of judgement from family).

To test this hypothesis, the independent variable assessed was between prior psychedelic use individuals and no prior psychedelic use individuals. The dependent variable was characterized by number of psychedelic concerns expressed between the two groups and which groups demonstrated greater or fewer concerns. This was accomplished through use of Mann-Whitney U.

Exploratory Hypothesis

Acceptance rates for the use of psychotherapeutics will directly correlate with discrete concerns about the therapeutic use of these compounds. To test this hypothesis, the first independent variable assessed was between individuals who support medical trials with psilocybin, ketamine and MDMA and individuals who do not. An additional independent variable was characterized by whether individuals in each group had discrete concerns regarding psychedelic use. This was accomplished through use of a nominal regression.

Bias, Problems and Alternative Strategies

While the secondary analysis of existing data is widely accepted and well-validated for research purposes, its use of previously collected data is subject to bias and confounding as researchers must decide what variables to use when the outcomes are known (Penson, 2006). Confounding occurs when a differential distribution of unmeasured variables exists among the samples used to create a secondary dataset and can cause associations to exist when there are none (Penson, 2006). Design variables used in the study were applied in the analysis in order to remove bias. Confounding was controlled through the utilization of random samples.

CHAPTER IV
ARTICLE MANUSCRIPT

Abstract

Substance use disorders (SUDs) present a rapidly evolving public health crisis and many individuals with SUDs fail to maintain abstinence despite adherence to current standard of care treatment options. Prior research has demonstrated compounds with unique psychoactive properties may improve ability to maintain abstinence across a variety of SUDs; examples of such compounds include psilocybin, ketamine, and 3,4-Methylenedioxymethamphetamine (MDMA). However, target population support for mental health treatment using these medications is unknown. In this study, a cross-sectional survey (n=919) was administered to analyze patient-level perspectives on the use of these novel psychotherapeutics for the treatment of SUDs. We hypothesized that individuals with SUDs would demonstrate differential acceptance of these treatment modalities as a function of prior awareness of these medications. The results showed that the majority of survey participants supported medical trials being conducted with psilocybin (72.1%), ketamine (71.6%), and MDMA (68.1%) in the future. Furthermore, survey respondents with prior knowledge of ketamine as a potential treatment option were significantly more in support of clinical trial research with ketamine compared to individuals without such prior awareness (3.96 vs 3.79; p= .005). However, there was no statistically significant difference in support for future research into psilocybin or MDMA based on prior knowledge of these potential treatment modalities. These results can be used to direct future research recruitment efforts and provide insight into clinical considerations that should be made when using these treatments.

Introduction

Substance use disorders (SUDs) are a rapidly evolving public health crisis. SUDs can lead to many adverse clinical consequences including contraction of infectious diseases, overdose, and the development of comorbid psychiatric disorders (World Drug Report, 2020). SUDs are classified on a range from mild to moderate to severe, with severity being dependent on how many criteria are met according to the Diagnostic and Statistical Manual of Mental Disorders (DSM). Criteria include physiologic changes (i.e. craving, tolerance, and withdrawal symptoms), psychosocial

problems (i.e. legal issues, occupational impairment, use in hazardous situations, decreased recreational enjoyment, family or social problems), and use despite harms to mental or physical well-being.

There are currently several medications for SUDs on the market today which have been granted FDA approval. These include pharmacotherapies for tobacco use disorder (TUD), alcohol use disorder (AUD) and opioid use disorder (OUD). While these SUDs can be treated with medications, many existing pharmacotherapies require daily adherence to medication self-administration, and long-term abstinence rates remain low (Mattick et al., 2001). In the case of OUD, there are currently only 2 main FDA approved medications authorized for treatment, methadone, or buprenorphine/naloxone (Subutex) (Butelman et al., 2017). Treatment with methadone may be used short-term in order to detoxify patients from opioids, however, it is also commonly used in long-term treatment provided the individual attends mandatory counseling due to the risks involved with methadone treatment (Butelman et al., 2017). Methadone can be fatal if taken in overdose and may also increase one's risk of severe liver disease with paired use of other substances such as alcohol or psychotropic medications like benzodiazepines and barbiturates (Kreek, Oratz, & Rothschild, 1978).

The opioid partial agonist medication, buprenorphine/naloxone (Subutex), has a lower risk or overdose than methadone due to its ceiling effect on respiratory depression (Butelman et al., 2017). Drug counseling is mandatory for treatment and patients must be seen at frequent intervals until a stable dosage is achieved (Butelman et al., 2017). This can lead to a significant reduction in long term abstinence rates due to patient drop out. Furthermore, individuals with co-occurring mental health disorders and substance use disorders report lower rates of treatment success, higher rates of psychiatric hospitalizations, and a higher prevalence of suicide (World Drug Report, 2020). It has been shown that only 18 % of addiction treatment programs and 9 % of mental health programs were able to provide pertinent treatment to dual diagnosis individuals in the United States

(McGovern et al., 2014). Additionally, there are currently no FDA-approved medications to treat stimulant use disorders (such as cocaine and amphetamines), benzodiazepine use disorder, or cannabis use disorder.

Novel psychoactive medications may improve ability to maintain abstinence across a broad variety of SUDs. A class of compounds with unique psychoactive effects called psychedelics, have shown early evidence of efficacy in the treatment of substance use disorders. In a dose dependent fashion, psychedelic compounds can temporarily produce dream-like states, altered sensory perceptions, and increased sense of universal connectedness. Unlike most existing SUD pharmacotherapies, these medications appear to improve ability to maintain abstinence across a wide spectrum of SUDs and may improve ability to maintain abstinence with only one or a few medication administrations (Curran et al., 2018). Evidence demonstrates that psychedelics have a high safety profile with extremely low levels of morbidity and mortality, and studies show limited evidence of any physical dependence (Johnson et al., 2018; Nichols, 2016). Psilocybin and 3,4-Methylenedioxymethamphetamine (MDMA) have been particularly well studied, and in the past three years, the FDA granted "breakthrough therapy" designation to these medications for treatment resistant depression and post-traumatic stress disorder (PTSD), respectively. Breakthrough therapy is granted when preliminary clinical data indicates that a drug intended to treat a serious medical condition has demonstrated substantial improvement over the currently available therapies (Commissioner, O., 2018).

Previous work has shown strong overall public support for research into this medication class (McCarriston, 2017). In a 2017 national survey of the general population, 53% of all respondents supported medical research into psychedelic drugs. A majority (63%) also said they would personally be open to medical treatment with psilocybin, ketamine, or MDMA if they had a medical condition for which it was proven effective and safe (McCarriston, 2017). However, it is unknown whether individuals with SUDs have similar levels of support. A majority of individuals

with SUDs will have tried more than one addictive substance, which suggests that they may have previously tried psychedelic compounds (McCance-Katz, 2019). However, SUDs are also characterized by avoidant thought processes however, and individuals often report using substances to cope with difficult feelings.

Given that psychedelic compounds can be associated with challenging psychoactive experiences, it is thus unclear whether individuals with SUDs will endorse a similar level of support to the general population, or whether they will endorse particular concerns about these prospective new treatment modalities.

Methods

Study Design and Recruitment

A cross-sectional survey study was designed and administered to 932 participants in order to analyze patient-level perspectives on the use of these novel psychotherapeutics for the treatment of SUDs. 12 participants did not complete the survey. Prior to completion of the main survey, potential participants were required to first complete a pre-screener questionnaire. This questionnaire evaluated several criteria for SUDs in order to ensure that only those self-reporting criteria matching that of a SUD would be offered the opportunity to complete the full survey. IP constraints were set up to prevent participants from taking the survey more than once.

Recruitment was conducted primarily through advertisements placed on the internet (i.e. Craigslist). Both pre-screening and the survey were conducted using the secure web database, REDCap. REDCap is primed to support online and offline data capture for research studies and operations. To have been considered for inclusion in the study, participants must have been (1) over the age of 18, of any gender, race or ethnicity, (2) able to comprehend English, (3) able to provide informed consent and function at an intellectual level sufficient to allow accurate completion of the

assessment instruments, (4) self-reporting at least 2 criteria for SUD, and (5) have used a substance of abuse at least once in the past month.

Screening and Informed Consent

Initial screening eligibility using the inclusion and exclusion criteria was conducted using a pre-screener questionnaire hosted via REDCap. Participants were informed that participation in the study was voluntary, and they could discontinue at any time. Participants were provided with an overview of the study procedures in advance.

Assessment Procedures

Following completion of informed consent, and provided that all inclusion and exclusion criteria were satisfied, eligible participants proceeded to take the "Opinions on Psychedelic Therapy" main survey. The survey took approximately 20 minutes to complete. The survey was anonymous, but participants were asked basic questions about themselves such as their age, gender, race, and use of alcohol and various substances. Participants went on to answer questions regarding (1) their level of support for the psychotherapeutics psilocybin, ketamine and MDMA being used in medical trials, (2) whether or not they believe these psychotherapeutics could be a beneficial treatment for people suffering with addictions, and (3) whether or not they themselves would be willing to participate in one of these trials. The psychotherapeutics psilocybin, ketamine, and MDMA were specifically chosen to asses individual level of support as there have been multiple prior studies conducted which demonstrate their efficacy in the treatment of addictions and other psychiatric disorders and thus they would be most likely to continue to be used in future medical trials.

Participants were then asked to select from a list of 14 concerns regarding the use of psychedelics (psilocybin, ketamine, MDMA, or other psychedelic medications) to reduce or stop using alcohol or other drugs. The concerns listed were comprised of common fears that are

associated with perceived possible consequences that might arise from taking a psychotherapeutic (fear of a bad trip, fear of losing one's mind, fear of job loss, etc.). Participants could select any number of concerns from this list or a "N/A" option if they had no concerns.

Participant Compensation

Participants were eligible to be compensated for their time with a $15 Amazon gift card. This gift card would be sent to their email address. If the participant did not wish to provide their email address, they may still take the survey, but they would not be able to receive compensation.

Data Analytic Procedure

All data from this survey was collected and managed using the secure REDCap (Research Electronic Data Capture) database. Furthermore, all data was analyzed using the SPSS statistical software platform. This study had the advantage of utilizing previously completed nationwide survey data in a large population (N=920). Baseline demographic characteristics were collected from all participants and descriptive statistics for the sample population were analyzed (Table 1).

While the secondary analysis of existing data is widely accepted and well-validated for research purposes, its use of previously collected data is subject to bias and confounding as researchers must decide what variables to use when the outcomes are known (Penson, 2006). Confounding occurs when a differential distribution of unmeasured variables exists among the samples used to create a secondary dataset and can cause associations to exist when there are none (Penson, 2006). Design variables used in the study were applied in the analysis in order to remove bias. Confounding was controlled through the utilization of random samples.

Results

Of the 920 individuals who completed the survey, 919 questionnaires were included in the study as one participant did not complete questions regarding their prior use of psychedelics. Our

research found the overall majority of survey participants supported medical trials being conducted with psilocybin (72.1%), ketamine (71.6%), and MDMA (68.1%) in the future (Table 2a-c; Figure 1a-c). To further determine acceptance rates of the use of psychedelics as a therapeutic modality among individuals self-reporting SUDs, we quantified the level of support for the use of psilocybin, ketamine and MDMA as a function of prior knowledge of these psychedelic medications. It was hypothesized that prior knowledge of these treatment modalities would have the greatest impact on the level of support for these treatments.

To test this hypothesis, the independent variable assessed was between prior psychedelic knowledge individuals and no prior psychedelic knowledge individuals. The dependent variable was characterized by the level of psychedelic support expressed between the two groups based on each individual's ranked choices regarding the use of psychedelics in medical research. This was accomplished through use of Mann-Whitney U due to a non-normal data distribution. Ketamine support scores were significant between participants with versus participants without prior awareness (3.96 vs 3.79; p=.005) (Table 3; Figure 2c-d), but there was no statistically significant difference regarding psilocybin or MDMA.

In addition, we were interested to characterize concerns about the therapeutic use of psychedelics among individuals self-reporting SUDs. Given that these medications have unique psychoactive effects, it was hypothesized that the number of concerns regarding the therapeutic use of psychedelics would be greatest in individuals who have never used psychedelics previously in contrast to those who had. It was further explored whether prior use affects the type of concerns expressed. The prediction was that individuals not reporting prior use would be more likely to endorse concerns related to the experience itself (i.e. fear of "going crazy") and that there would be no difference between groups on psychosocial concerns (i.e. fear of judgement from family).

To test this hypothesis, the independent variable assessed was between prior psychedelic use individuals and no prior psychedelic use individuals. The dependent variable was characterized

by total number of psychedelic concerns expressed between the two groups and which groups demonstrated greater or fewer concerns. This was accomplished through use of Mann-Whitney U due to a non-normal data distribution. There was no statistically significant difference found between an individual's prior psychedelics use and overall concerns, having concerns related to the experience itself, nor a difference between groups regarding psychosocial concerns (Figure 3a-c).

Additionally, our group went on to explore whether acceptance rates for the use of psychotherapeutics would directly associate with discrete concerns about the therapeutic use of these compounds. To test this, the first independent variable assessed was between individuals who support medical trials with psilocybin, ketamine and MDMA and individuals who do not. An additional independent variable was characterized by whether individuals in each group had discrete concerns regarding psychedelic use. This was accomplished using nominal regression.

For psilocybin, one concern was identified to be significantly correlated with an individual's level of support for medical trials being conducted with psilocybin in the future. For each unit of support increased, the odds of not selecting the concern "Fear that you would lose your sense of self" increased by 1.299 (95% CI, 1.063 to 1.588) times, a statistically significant effect, $p = .011$ (Table 5a). For Ketamine, two concerns were identified to be significantly correlated with an individual's level of support for trying ketamine treatment themselves. For each unit of support increased, the odds of not selecting the concern "Fear that it would change you" increased by 1.207 (95% CI, 1.009 to 1.444) times, a statistically significant effect, $p = .039$ (Table 5b). For each unit of support increased, the odds of not selecting the concern "Fear that you would harm yourself or others while on a bad trip" increased by 1.211 (95% CI, 1.009 to 1.453) times, a statistically significant effect, $p = .040$ (Table 5b). Additionally, one concern was significantly correlated with an individual's level of support for ketamine treatment being beneficial for people with SUDs. For each unit of support increased, the odds of not selecting the concern "Fear that you would feel guilt

during your trip" increased by 1.233 (95% CI, 1.014 to 1.500) times, a statistically significant effect, p = .035 (Table 5b).

For MDMA, two concerns were identified to be significantly correlated with an individual's level of support for medical trials with MDMA being conducted in the future. For each unit of support reduction, the odds of not selecting the concern "Fear that it would cause you to "go crazy" or "lose your mind"" increased by 0.774 (95% CI, 0.648 to 0.925) times, a statistically significant effect, p = .005 (Table 5c). For each unit of support reduction, the odds of not selecting the concern "Fear that you would harm yourself or others while on a bad trip" increased by 0.791 (95% CI, 0.658 to 0.951) times, a statistically significant effect, p = .013 (Table 5c). Two additional concerns were identified to be significantly correlated with an individual's level of support for MDMA being beneficial for people with a SUD. For each unit of support reduction, the odds of not selecting the concern "Fear that you would lose your sense of self" increased by 0.749 (95% CI, 0.618 to 0.908) times, a statistically significant effect, p = .003 (Table 5c). For each unit of support reduction, the odds of not selecting the concern "Fear that it would affect your employment" increased by 0.770 (95% CI, 0.630 to 0.941) times, a statistically significant effect, p = .011 (Table 5c). Finally, two concerns were identified to be significantly correlated with an individual's level of support for trying MDMA themselves if treatment was appropriate. For each unit of support reduction, the odds of not selecting the concern "Fear that you would feel guilt during your trip" increased by 0.843 (95% CI, 0.740 to 0.960) times, a statistically significant effect, p = .010 (Table 5c). For each unit of support reduction, the odds of not selecting the concern "Fear that it would affect your employment" increased by 0.862 (95% CI, 0.751 to 0.990) times, a statistically significant effect, p = .036 (Table 5c).

Discussion

There is a clear need for novel, efficacious pharmacotherapies for treatment of SUDs. While pharmacotherapies exist for certain SUDs, most current medications require daily adherence

to self-administration, and long-term abstinence rate remain low. Additionally, there are currently no FDA-approved medications to treat stimulant use disorders (such as cocaine, amphetamines), benzodiazepine use disorder and cannabis use disorder. Multiple prior studies including both randomized controlled trials and naturalistic studies suggest that these psychotherapeutic medications have potential therapeutic benefit in the treatment of addictions and other psychiatric disorders. These compounds are associated with a high safety profile with extremely low levels of morbidity and mortality, and limited evidence of any physical dependence.

A 2017 national survey of the general population by the data analytic group, YouGov, found that the majority of respondents supported future medical research into psilocybin (63%), ketamine (61%), and MDMA (61%) (McCarriston, 2017). A majority (63%) also said they would personally be open to medical treatment with psilocybin, ketamine, or MDMA if they had a medical condition for which it was proven effective and safe (McCarriston, 2017).

Until now it had been unknown whether individuals with SUDs would demonstrate similar levels of support. While multiple previous clinical trials have been conducted using psychedelics in an attempt to treat patients with a SUD, individuals already involved in psychedelic therapy research may not display the same attitudes and opinions with SUD individuals who have not received these therapies. This study found that the overall majority of survey participants with a SUD demonstrated a greater support for medical trials being conducted with psilocybin (72.1%), ketamine (71.6%), and MDMA (68.1%) in the future as compared to the general population (Table 2a-c; Figure 1a-c). Additionally, it was discovered that the overall majority of survey participants with a SUD demonstrated a greater support for personally being open to medical treatment with psilocybin (75.6%), ketamine (74.3%), or MDMA (58.9%) if they had a medical condition for which it was proven effective and safe as compared to the general population (Table 4a-c; Figure 4a-c). It is important to note that most respondents (87%) in this study reported personal prior use of psychedelics in the past and more work needs to be done to determine whether this plays a role

in an individual's acceptance. Moreover, this study did not investigate whether participants who had previously tried psychedelics had ever done so in an attempt to self-medicate. Multiple prior studies have shown that individuals who have used psychedelics to self-medicate for a variety of mental health disorders in the past, report psychedelics to be more efficacious at treating their symptoms compared to conventional treatments offered by medical professionals (Mason, N. L., & Kuypers, K. P. C. (2018), Hutten NR et al. (2019), Lea, T. et al. (2020)). It would be beneficial for future research to assess whether support differs with individuals who utilized psychedelics to self-medicate in the past.

When investigating the impact prior awareness of psychedelic research had on support levels, it was found that ketamine support scores were significantly different between participants with versus participants without prior awareness (3.96 vs 3.79; p= .005) (Table 3; Figure 2c-d), but there was no statistically significant difference regarding psilocybin or MDMA. This difference in ketamine support scores could be explained by the fact that ketamine does not fall into the category of classic psychedelic and is more well-known for its dissociative properties. While statistical significance regarding ketamine support was reached, it is argued that a difference in support score of 3.96 vs 3.79 still demonstrates an overall acceptance of future research with or without prior awareness.

It was further investigated whether individuals who had indicated prior use of psychedelics would differ in the number and types of concerns expressed regarding psychedelic therapies from individuals who had indicated no prior use of psychedelics. The data show there were no significant differences between prior use vs no prior use groups regarding the number and types of concerns expressed. While there was no significance reached, this is still beneficial information that can help direct future research recruitment efforts and clinical considerations using these treatments. Finally, in an effort to explore whether acceptance rates would directly correlate with discrete concerns regarding the therapeutic use of psychedelics, it was discovered that there were a handful of

concerns which significantly affected an individual's level of support. It is beneficial for future studies to be aware of how these concerns correlate with individual's acceptance rates so that an effort can be made to properly address them and adequately inform the public.

This study provides essential information that will direct future research recruitment efforts and clinical considerations using these treatments and will inform future studies for this urgent public health need. There are numerous potential directions that can and should be investigated by future studies. Investigating how additional key demographics such as age, gender, race, education, etc. vary with individual levels of support would be an excellent starting point. Additionally, the majority of participants in this study were poly substance users, meaning they potentially suffered from multiple SUDs which may have had an impact on acceptance rates. One of the biggest challenge's psychedelic research faces today is reversing the stigma that has been placed on these substances for decades. Future research should be prepared to investigate how political affiliation affects an individual's level of support as that information will prove to be extremely vital in implementing policy change and advancing science and medicine for the benefit of patients.

Table 1. Participant Demographics

Age	**n (%)**
18 to 24	80 (8.7)
25 to 34	447 (48.6)
35 to 44	357 (38.8)
45 to 54	29 (3.2)
55+	6 (0.7)
Gender	
Male	651 (70.9)
Female	259 (28.2)
Transgender or non-binary	4 (0.4)
Other or prefer not to answer	4 (0.4)
Region	
Northeast	205 (22.3)
Midwest	210 (22.9)
South	231 (25.1)
West	273 (29.7)
Community	
Large city	406 (44.2)
Midsized city	293 (31.9)
Small city	180 (19.6)
Suburban	35 (3.8)
Rural	5 (0.5)
Education	
No high school	5 (0.5)
Some high school	12 (1.3)
High school graduate or have GED	84 (9.1)
Some college	95 (10.3)
Completed two-year college degree	218 (23.7)
Completed four-year college degree	388 (42.2)
Have had some graduate degree training	31 (3.4)
Have completed graduate degree training	86 (9.4)

Relationship	
Married	619 (67.4)
Never married	147 (16.0)
Separated	59 (6.4)
Divorced	44 (4.8)
Domestic/civil partnership	38 (4.1)
Widowed	12 (1.3)
Children	
Yes	646 (70.3)
No	273 (29.7)
Race	
White	528 (57.5)
Black or African American	191 (20.8)
Hispanic or Latino	137 (14.9)
American Indian or Alaskan Native	47 (5.1)
Asian	26 (2.8)
Native Hawaiian or Pacific Islander	7 (0.8)
Other or prefer not to answer	3 (0.3)
Substance of abuse	
Alcohol	569 (61.9)
Marijuana	566 (61.6)
Tobacco	544 (59.2)
Cocaine	234 (25.5)
Opiates	143 (15.6)
Amphetamines	133 (14.5)
Benzodiazepines	112 (12.2)
Other	6 (0.7)
Number of substances used per month	
1	396 (0.43)
2	126 (0.14)
3	187 (0.20)
4	90 (0.10)
>5	120 (0.13)

Table 2a. Overall Psilocybin Research Level of Support

Based on these preliminary findings, and anything else you may know: Do you support or oppose similar medical trials with psilocybin being conducted in the future?				
	Frequency	Percent	Valid Percent	Cumulative Percent
Strongly oppose	5	0.5	0.5	0.5
Oppose	23	2.5	2.5	3.0
Neutral or unsure	228	24.8	24.8	27.9
Support	432	47.0	47.0	74.9
Strongly support	231	25.1	25.1	100.0
Total	919	100.0	100.0	

Table 2b. Overall Ketamine Research Level of Support

Based on these preliminary findings, and anything else you may know: Do you support or oppose similar medical trials with ketamine being conducted in the future?				
	Frequency	Percent	Valid Percent	Cumulative Percent
Strongly oppose	5	0.5	0.5	0.5
Oppose	44	4.8	4.8	5.3
Neutral or unsure	212	23.1	23.1	28.4
Support	432	47.0	47.0	75.4
Strongly support	226	24.6	24.6	100.0
Total	919	100.0	100.0	

Table 2c. Overall MDMA Research Level of Support

Based on these findings and what you may have known previously, do you support or oppose similar medical trials with MDMA being conducted in the future?				
	Frequency	Percent	Valid Percent	Cumulative Percent
Strongly oppose	9	1.0	1.0	1.0
Oppose	41	4.5	4.5	5.4
Neutral or unsure	243	26.4	26.4	31.9
Support	387	42.1	42.1	74.0
Strongly support	239	26.0	26.0	100.0
Total	919	100.0	100.0	

Table 3. Prior Awareness vs Research Level of Support

	Based on these preliminary findings, and anything else you may know: Do you support or oppose similar medical trials with psilocybin being conducted in the future?	Based on these preliminary findings, and anything else you may know: Do you support or oppose similar medical trials with ketamine being conducted in the future?	Based on these findings and what you may have known previously, do you support or oppose similar medical trials with MDMA being conducted in the future?
Mann-Whitney U	94893.000	85426.000	91297.000
Wilcoxon W	145296.000	135829.000	141700.000
Z	-0.147	-2.802	-1.142
Asymp. Sig. (2-tailed)	0.883	0.005	0.253

a. Grouping Variable: Have you ever previously heard about the use of psychedelic-type substances (such as psilocybin, LSD, peyote, ibogaine, ayahuasca, and ketamine) being used in the treatment of addictions?

Table 4a. Overall Psilocybin "Would Try" Level of Support

If psilocybin is proven to be safe and effective for the treatment of addictions, would you or would you not try this treatment if it was appropriate for you?				
	Frequency	Percent	Valid Percent	Cumulative Percent
Definitely not	8	0.9	0.9	0.9
Probably not	20	2.2	2.2	3.0
Neutral or unsure	197	21.4	21.4	24.5
Probably would	404	44.0	44.0	68.4
Definitely would	290	31.6	31.6	100.0
Total	919	100.0	100.0	

Table 4b. Overall Ketamine "Would Try" Level of Support

If ketamine is proven to be safe and effective for treatment after further trials, would you or would you not try this treatment if it was appropriate for you?				
	Frequency	Percent	Valid Percent	Cumulative Percent
Definitely not	9	1.0	1.0	1.0
Probably not	36	3.9	3.9	4.9

Neutral or unsure	192	20.9	20.9	25.8
Probably would	403	43.9	43.9	69.6
Definitely would	279	30.4	30.4	100.0
Total	919	100.0	100.0	

Table 4c. Overall MDMA "Would Try" Level of Support

If MDMA is proven to be safe and effective for treatment after further trials, would you or would you not try this treatment if it was appropriate for you?				
	Frequency	Percent	Valid Percent	Cumulative Percent
Definitely would	226	24.6	24.6	24.6
Probably would	315	34.3	34.3	58.9
Neutral or unsure	224	24.4	24.4	83.2
Probably would not	88	9.6	9.6	92.8
Definitely would not	66	7.2	7.2	100.0
Total	919	100.0	100.0	

Table 5a. Psilocybin Concerns vs Support

Question:	Based on these preliminary findings, and anything else you may know: Do you support or oppose similar medical trials with psilocybin being conducted in the future?	B	Std. Error	Wald	df	Sig.	Exp(B)	95% Confidence Interval for Exp(B)	
								Lower Bound	Upper Bound
Concern:	Fear that you would lose your sense of self	0.261	0.102	6.519	1	0.011	1.299	1.063	1.588

Table 5b. Ketamine Concerns vs Support

Question:	If ketamine is proven to be safe and effective for treatment after further trials, would you or would you not try this treatment if it was appropriate for you?	B	Std. Error	Wald	df	Sig.	Exp(B)	95% Confidence Interval for Exp(B)	
								Lower Bound	Upper Bound
Concern:	Fear that it would "change you"	0.188	0.091	4.258	1	0.039	1.207	1.009	1.444
	Fear that you would harm yourself or others while on a bad trip	0.191	0.093	4.228	1	0.040	1.211	1.009	1.453
Question:	Do you think ketamine could be a beneficial treatment for people suffering with addictions?	B	Std. Error	Wald	df	Sig.	Exp(B)	95% Confidence Interval for Exp(B)	
								Lower Bound	Upper Bound
Concern:	Fear that you would feel guilt during your trip	0.210	0.100	4.424	1	0.035	1.233	1.014	1.500

Table 5c. MDMA Concerns vs Support

Based on these findings and what you may have known previously, do you support or oppose similar medical trials with MDMA being conducted in the future?	B	Std. Error	Wald	df	Sig.	Exp(B)	95% Confidence Interval for Exp(B)	
							Lower Bound	Upper Bound
Fear that it would cause you to "go crazy" or "lose your mind"	-0.256	0.091	7.934	1	0.005	0.774	0.648	0.925
Fear that you would harm yourself or others while on a bad trip[a]	-0.235	0.094	6.214	1	0.013	0.791	0.658	0.951
Do you think MDMA could or could not be a beneficial treatment for people suffering with PTSD?	B	Std. Error	Wald	df	Sig.	Exp(B)	95% Confidence Interval for Exp(B)	
							Lower Bound	Upper Bound
Fear that you would lose your sense of self	-0.289	0.098	8.697	1	0.003	0.749	0.618	0.908
Fear that it would affect your employment	-0.261	0.102	6.514	1	0.011	0.770	0.630	0.941
If MDMA is proven to be safe and effective for treatment after further trials, would you or would you not try this treatment if it was appropriate for you?	B	Std. Error	Wald	df	Sig.	Exp(B)	95% Confidence Interval for Exp(B)	
							Lower Bound	Upper Bound
Fear that you would feel guilt during your trip	-0.171	0.066	6.626	1	0.010	0.843	0.740	0.960
Fear that it would affect your employment	-0.148	0.071	4.409	1	0.036	0.862	0.751	0.990

Figure 1a. Overall Psilocybin Research Level of Support

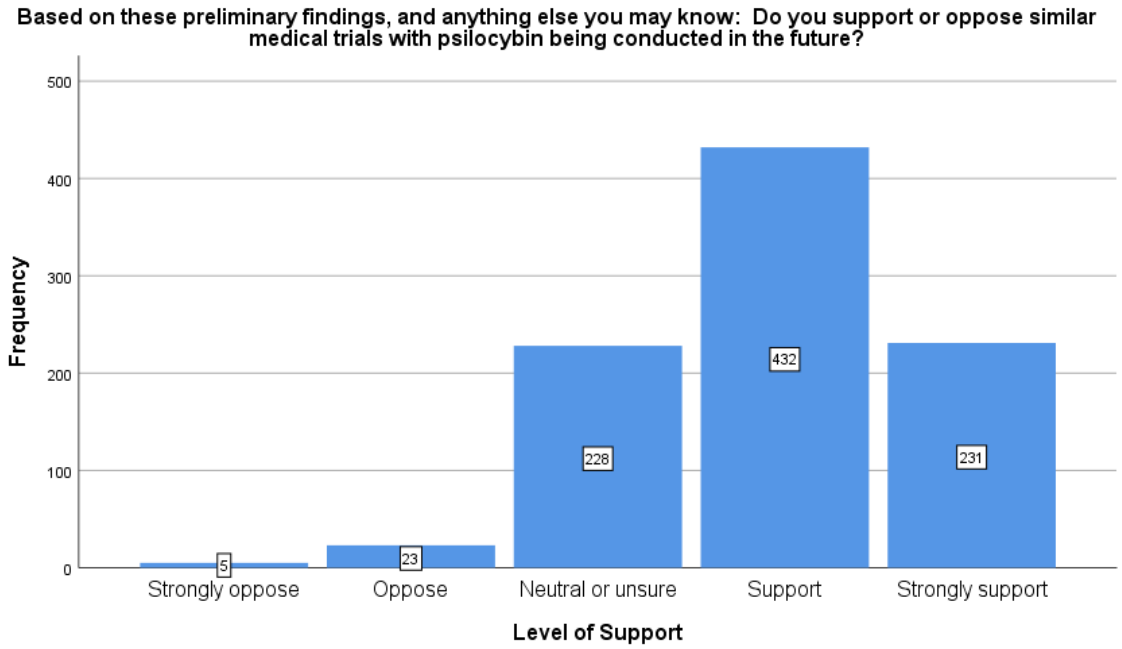


Figure 1b. Overall Ketamine Research Level of Support

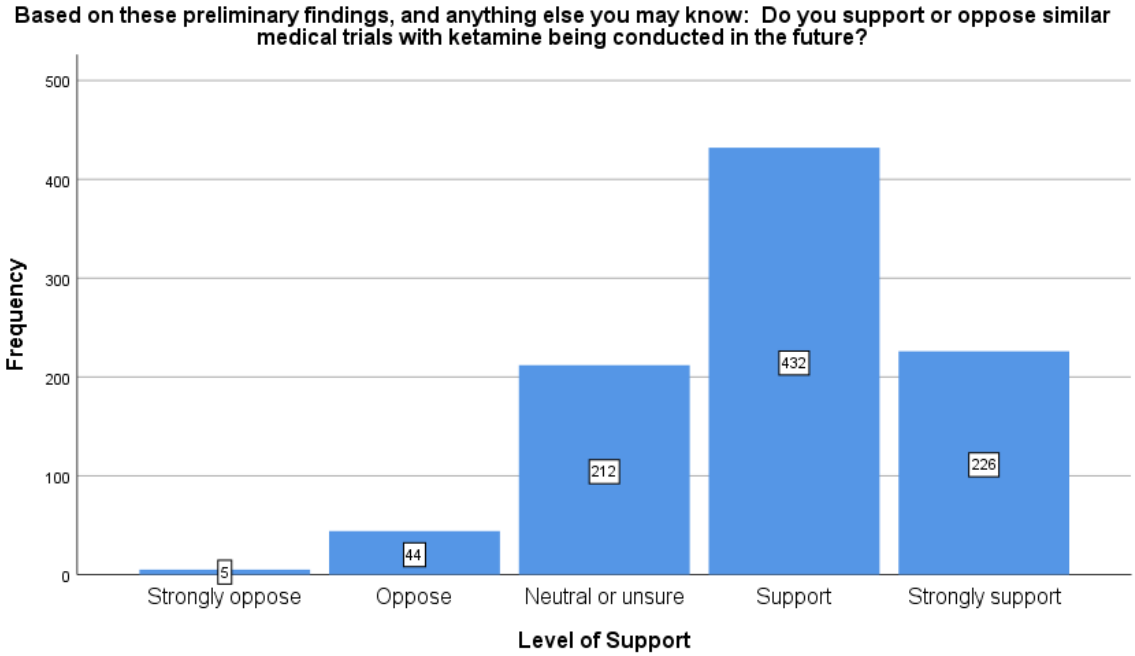


Figure 1c. Overall MDMA Research Level of Support

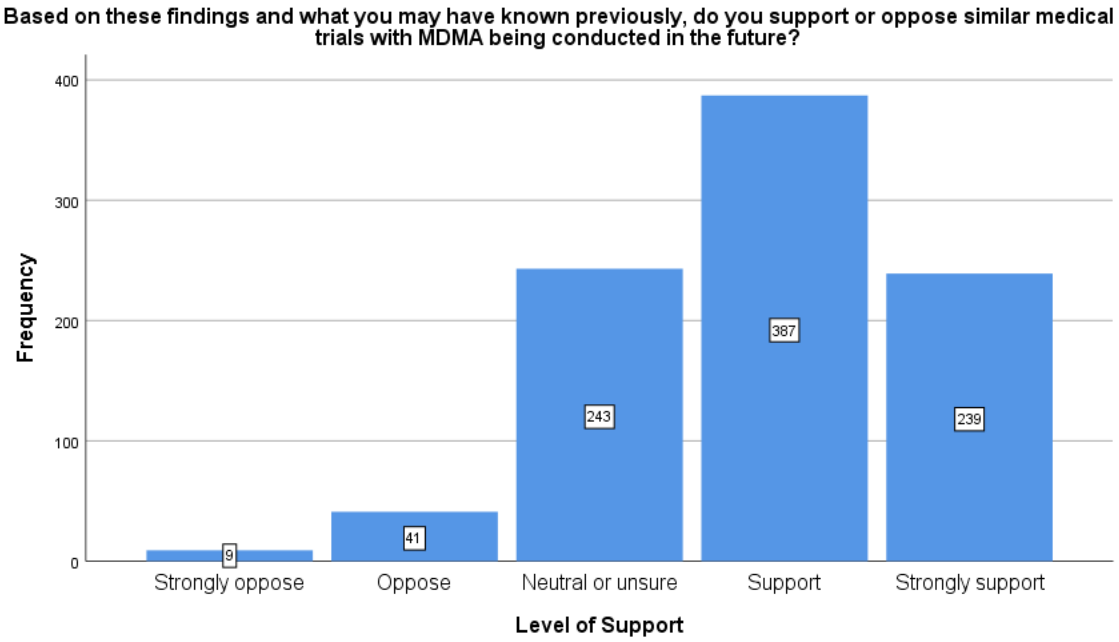


Figure 2a. Psilocybin Research Support vs Prior Awareness

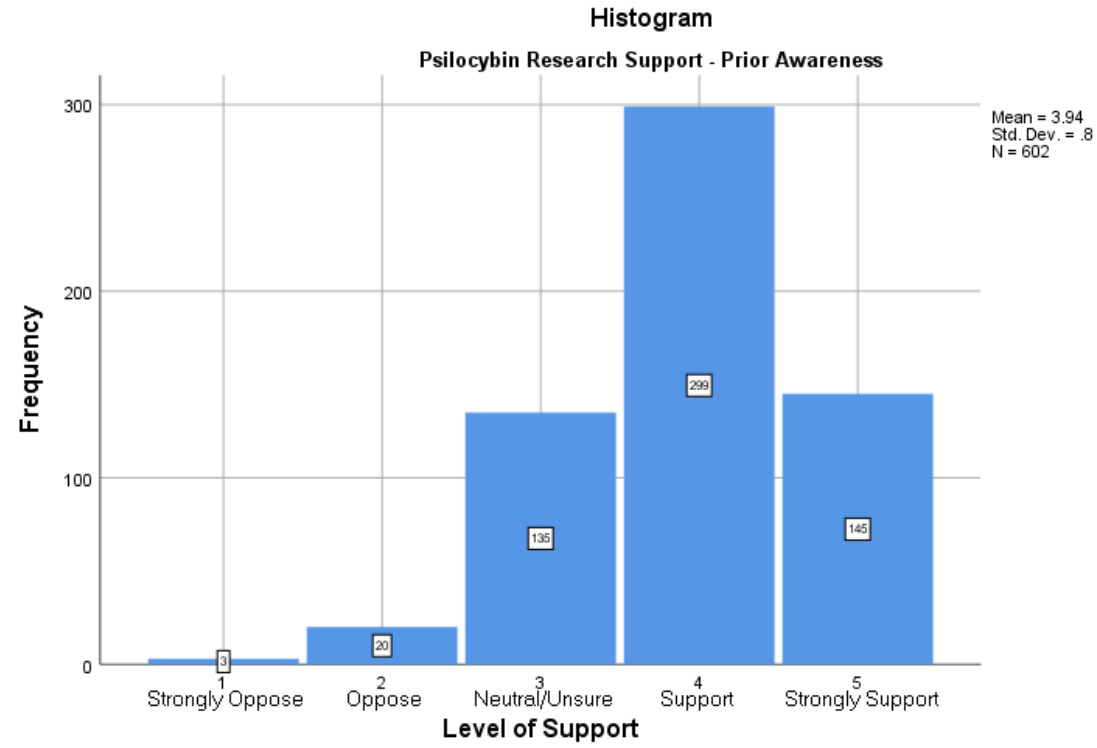


Figure 2b. Psilocybin Research Support vs No Prior Awareness

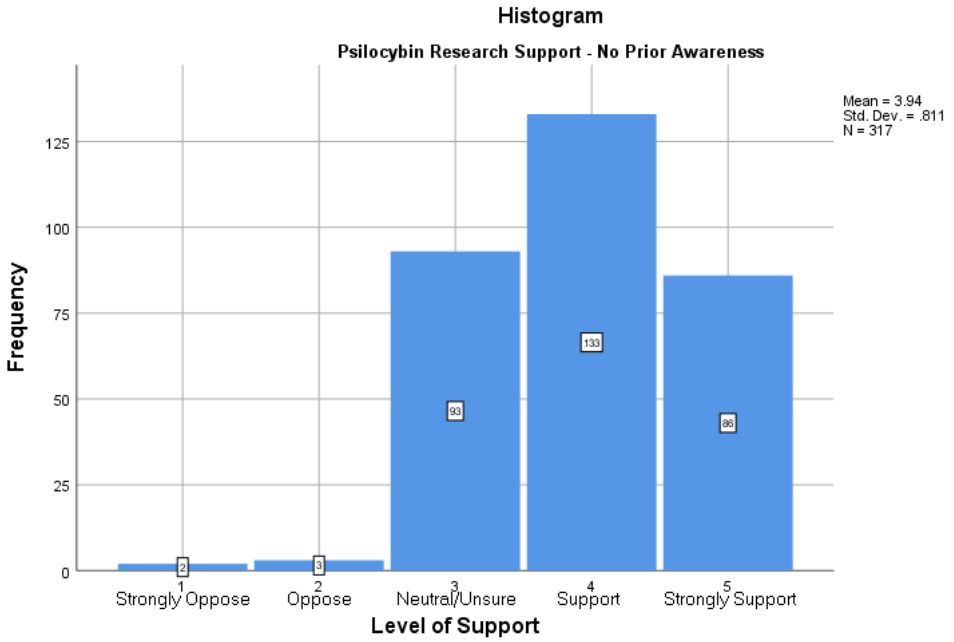


Figure 2c. Ketamine Research Support vs Prior Awareness

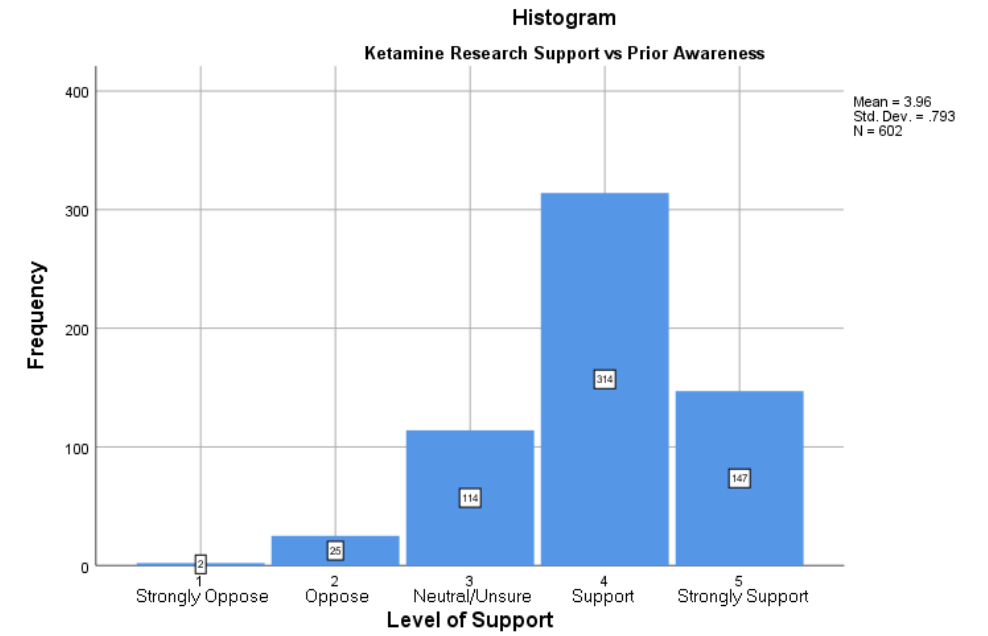


Figure 2d. Ketamine Research Support vs No Prior Awareness

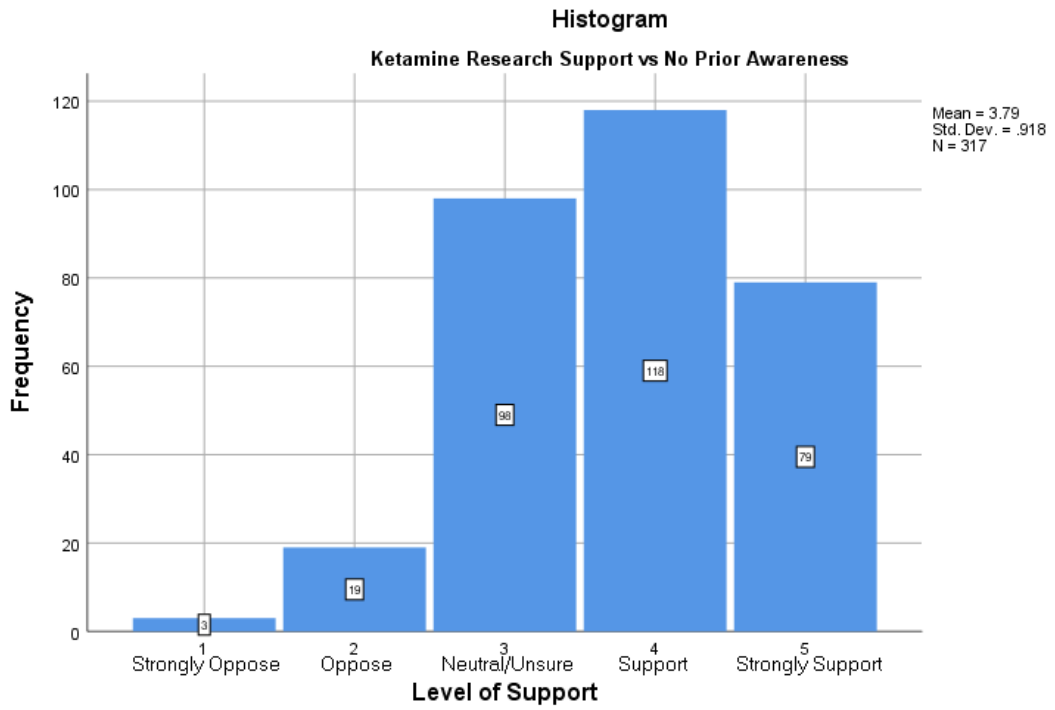


Figure 2e. MDMA Research Support vs Prior Awareness

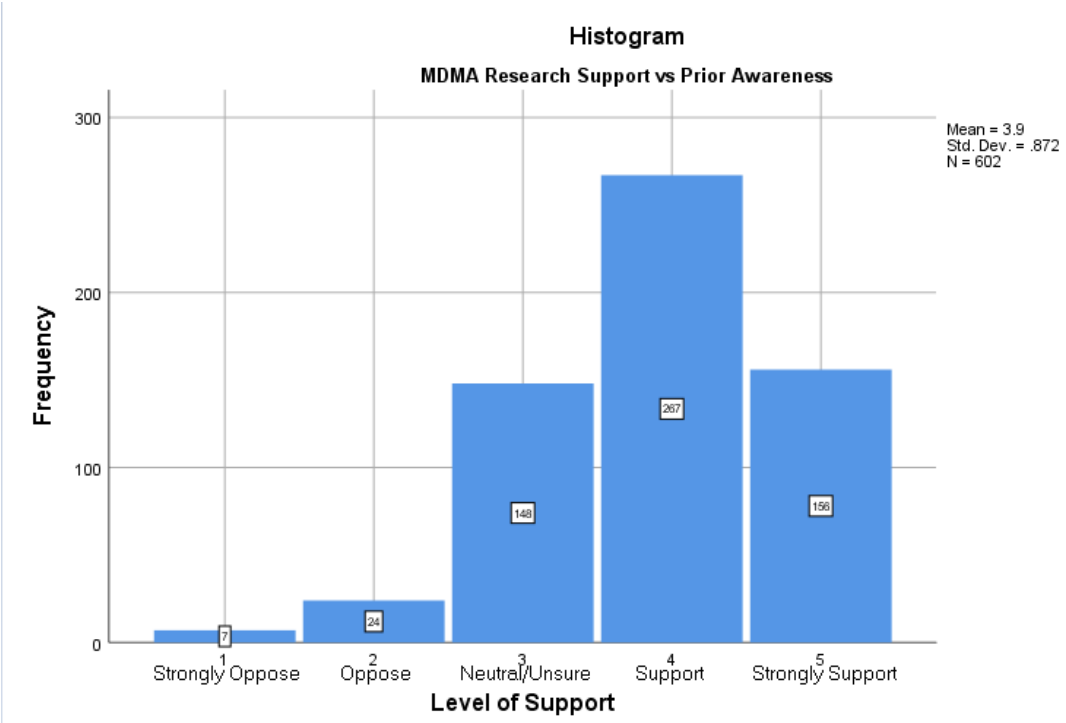


Figure 2f. MDMA Research Support vs No Prior Awareness

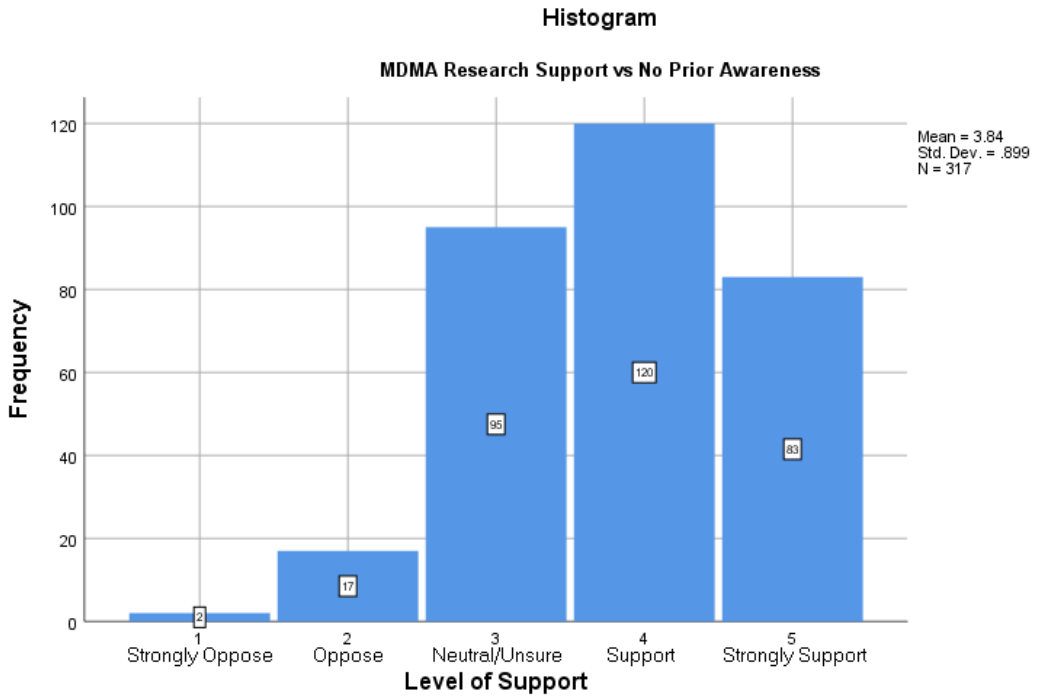
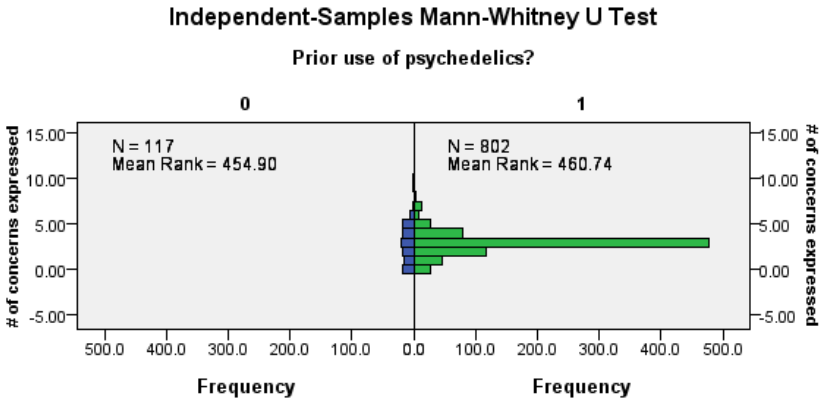
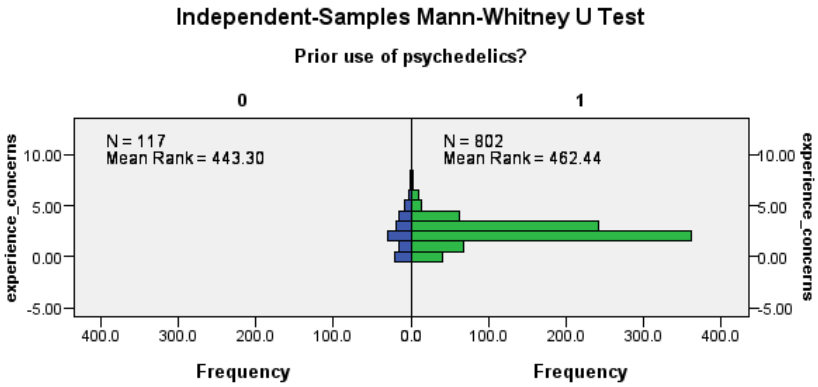


Figure 3a. Prior Use vs Concerns Overall



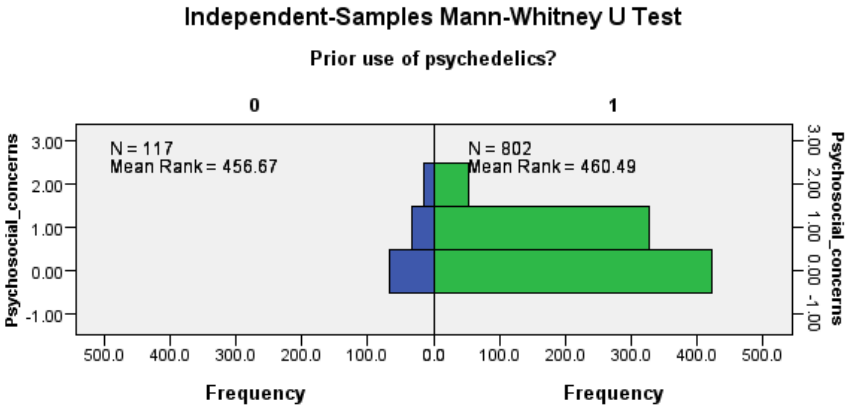
Total N	919
Mann-Whitney U	47,514.000
Wilcoxon W	369,517.000
Test Statistic	47,514.000
Standard Error	2,452.390
Standardized Test Statistic	.243
Asymptotic Sig. (2-sided test)	.808

Figure 3b. Prior Use vs Experience Concerns



Total N	919
Mann-Whitney U	48,870.500
Wilcoxon W	370,873.500
Test Statistic	48,870.500
Standard Error	2,541.848
Standardized Test Statistic	.769
Asymptotic Sig. (2-sided test)	.442

Figure 3c. Prior Use vs Psychosocial Concerns



Total N	919
Mann-Whitney U	47,306.500
Wilcoxon W	369,309.500
Test Statistic	47,306.500
Standard Error	2,380.025
Standardized Test Statistic	.164
Asymptotic Sig. (2-sided test)	.870

Figure 4a. Overall Psilocybin "Would Try" Level of Support

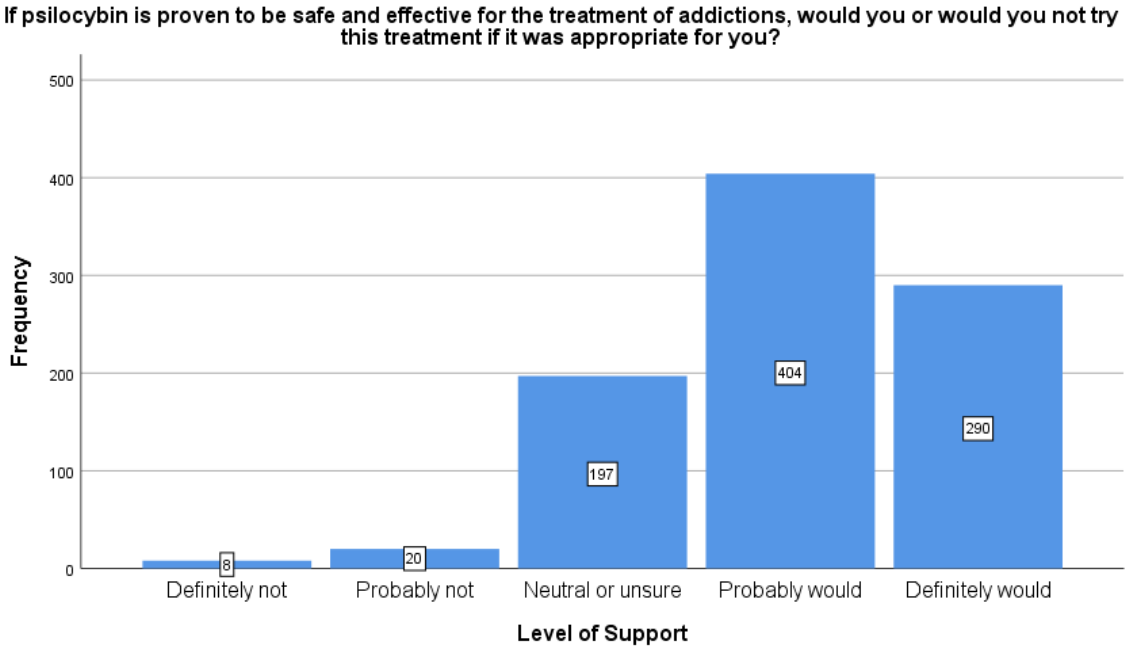


Figure 4b. Overall Ketamine "Would Try" Level of Support

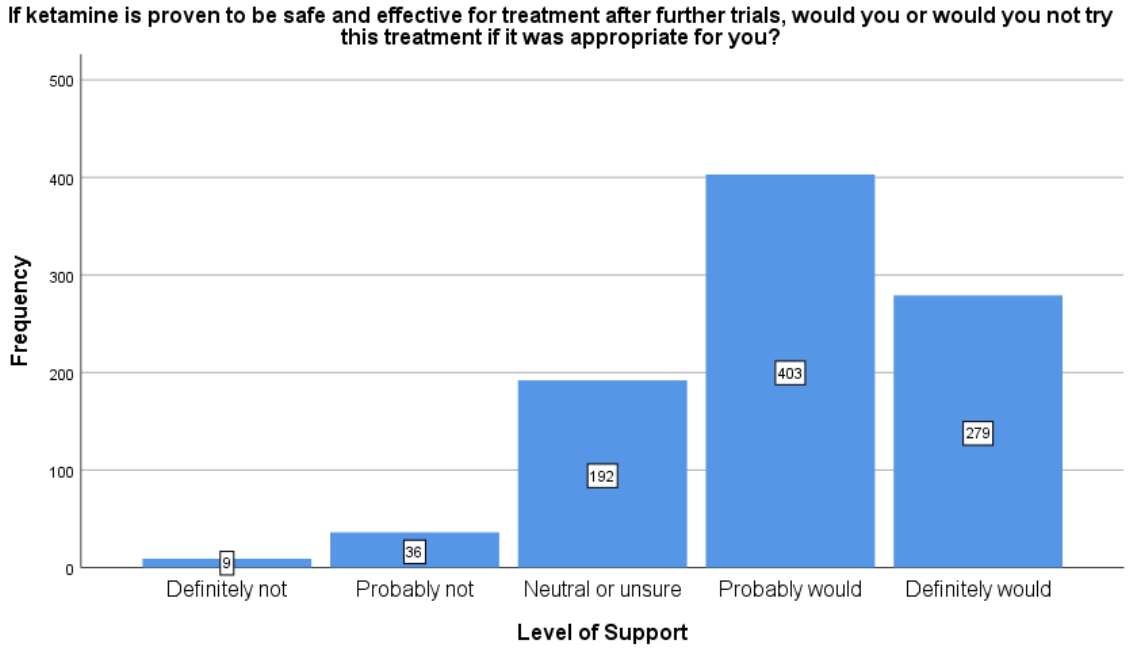
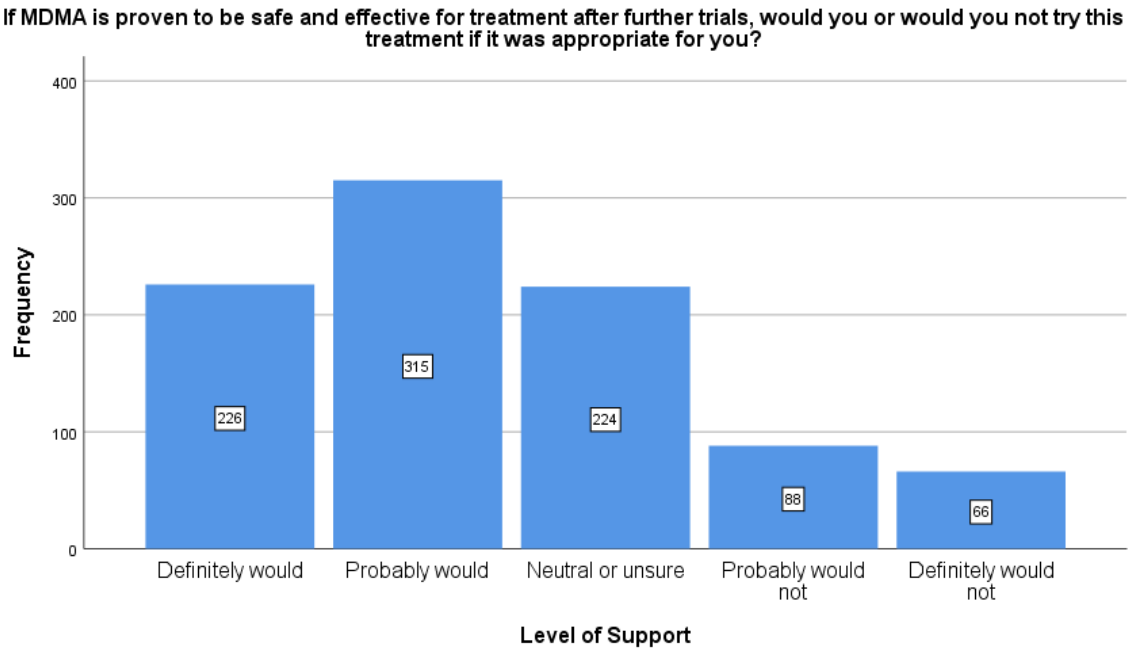


Figure 4c. Overall MDMA "Would Try" Level of Support



REFERENCES

Baker, A., Lee, N.K. & Jenner, L. (Eds) (2004). Models of intervention and care for psychostimulant users, 2nd Edition, National Drug Strategy Monograph Series No. 51. Canberra. Australian Government Department of Health and Ageing.

Bas T.H. de Veen, Arnt F.A. Schellekens, Michel M.M. Verheij & Judith R. Homberg (2017). Psilocybin for treating substance use disorders?, Expert Review of Neurotherapeutics,17:2, 203-212, DOI: 10.1080/14737175.2016.1220834

Berman, R. M., Cappiello, A., Anand, A., Oren, D. A., Heninger, G. R., Charney, D. S., & Krystal, J. H. (2000). *Antidepressant effects of ketamine in depressed patients. Biological Psychiatry, 47(4), 351–354.* doi:10.1016/s0006-3223(99)00230-9

Bogenschutz MP, Forcehimes AA, Pommy JA, Wilcox CE, Barbosa PC, Strassman RJ. (2015) Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study. J Psychopharmacol. 2015 Mar;29(3):289-99. doi: 10.1177/0269881114565144. Epub 2015 Jan 13. PMID: 25586396.

Butelman ER, Kreek MJ. Medications for substance use disorders (SUD): emerging approaches. Expert Opin Emerg Drugs. 2017;22(4):301-315. doi:10.1080/14728214.2017.1395855

Cheng HG, Phillips MR. Secondary analysis of existing data: opportunities and implementation. Shanghai Arch Psychiatry. 2014;26(6):371-375. doi: 10.11919/j.issn.1002-0829.214171

Commissioner, O. (2018, January 4). Breakthrough Therapy. https://www.fda.gov/patients/fasttrack-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy

Commissioner, O. (2019, March 5). FDA approves new nasal spray medication for treatment resistant depression; available only at a certified doctor's office or clinic. Retrieved December 16, 2020, from https://www.fda.gov/news-events/press-announcements/fdaapproves-new-nasal-spray-medication-treatment-resistant-depression-available-onlycertified

Curran, H.V., Nutt, D. & de Wit, H. Psychedelics and related drugs: therapeutic possibilities, mechanisms and regulation. Psychopharmacology 235, 373–375 (2018). https://doi.org/10.1007/s00213-017-4822-3

Davis AK, Barrett FS, May DG, Cosimano MP, Sepeda ND, Johnson MW, Finan PH, Griffiths RR. (2020) Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial. JAMA Psychiatry. 2020 Nov 4:e203285. doi: 10.1001/jamapsychiatry.2020.3285. Epub ahead of print. Erratum in: JAMA Psychiatry. 2021 Feb 10;: PMID: 33146667; PMCID: PMC7643046.

Himmelseher, S., & Pfenninger, E. (2008, January 22). Die klinische Anwendung von S-(+) Ketamin - eine Standortbestimmung. Retrieved December 16, 2020, from https://www.thieme-connect.de/products/ejournals/abstract/10.1055/s-2007-994851

Hutten NR, Mason NL, Dolder PC and Kuypers KP(2019) Self-rated effectiveness of microdosing withpsychedelics for mental and physical health problems amongst microdosers. Front. Psychiatry 10:672.doi:10.3389/fpsyt.2019.00672

Jansen, K. L. R. (2000). A Review of the Nonmedical Use of Ketamine: Use, Users and Consequences. Journal of Psychoactive Drugs, 32(4), 419–433. doi:10.1080/02791072.2000.10400244

Johnson MW, Garcia-Romeu A, Cosimano MP, Griffiths RR. (2014) Pilot study of the 5-HT2AR agonist psilocybin in the treatment of tobacco addiction. Journal of Psychopharmacology. 2014;28(11):983-992. doi:10.1177/0269881114548296

Johnson, MW, Griffiths, RR, Hendricks, PS, et al. (2018) The abuse potential of medical Psilocybin according to the 8 factors of the controlled substances act. Neuropharmacology 142: 143166.

Jones JL, Mateus CF, Malcolm RJ, Brady KT, Back SE. Efficacy of Ketamine in the Treatment of Substance Use Disorders: A Systematic Review. *Front Psychiatry*. 2018; 9:277. Published2018 Jul 24. doi:10.3389/fpsyt.2018.00277

Kalant, H. (2001). The pharmacology and toxicology of 'ecstasy' (MDMA) and related drugs. Canadian Medical Association Journal, 165(7), 917–928.

Koob GF, Volkow ND. Neurobiology of addiction: a neurocircuitry analysis. Lancet Psychiatry. 2016;3(8):760-773. doi:10.1016/S2215-0366(16)00104-8

Kreek MJ, Oratz M, Rothschild MA, Gastroenterology. 1978 Jul; 75(1):88-94.

Lea, T., Amada, N., Jungaberle, H. et al. Perceived outcomes of psychedelic microdosing as self-managed therapies for mental and substance use disorders. Psychopharmacology 237, 1521–1532 (2020). https://doi.org/10.1007/s00213-020-05477-0

Lyke Jennifer. Chapter 81 - Psilocybin and Peak Experiences. Editor(s): Victor R. Preedy. Neuropathology of Drug Addictions and Substance Misuse. Academic Press. 2016. Pages866-874. ISBN 9780128002124. https://doi.org/10.1016/B978-0-12-800212 4.00081-9.

M.A.P.S. (December 16, 2020) Phase 3 Program: MDMA-Assisted Psychotherapy for PTSD. (n.d.). Retrieved, from https://maps.org/research/mdma/ptsd/phase3

Mason, N. L., & Kuypers, K. P. C. (2018). Mental health of a self-selected sample of psychedelic users and self-medication practices with psychedelics, Journal of Psychedelic Studies , 2(1), 45-52. Retrieved Apr 23, 2021, from https://akjournals.com/view/journals/2054/2/1/article-p45.xml

Mattick RP, Digiusto E, Doran CM, O'Brien S,Shanahan M, Kimber J, Henderson N, Breen C,Shearer J, Gates J, Shakeshaft A and NEPOD Trial Investigators, 2001. National Evaluation of Pharmacotherapies for Opioid Dependence:Report of Results and Recommendations. National Drug and Alcohol Research Centre,Sydney.

McCance-Katz, E. F. (2019). The national survey on drug use and health: 2017. Substance Abuse and Mental Health Services Administration. https://www. samhsa. gov/data/sites/default/files/nsduh-ppt-09-2018. pdf. Accessed May, 7.

McCarriston, G. (2017, June 23). Majority of Americans ready to embrace psychedelic therapy. https://today.yougov.com/topics/lifestyle/articles-reports/2017/06/23/americans-readyembrace-psychedelic-therapy

Mithoefer, M. C., Wagner, M. T., Mithoefer, A. T., Jerome, L., Martin, S. F., Yazar-Klosinski, B., Doblin, R. (2012). Durability of improvement in post-traumatic stress disorder symptoms and absence of harmful effects or drug dependency after 3,4 methylenedioxymethamphetamine-assisted psychotherapy: a prospective long-term follow-up study. Journal of Psychopharmacology, 27(1), 28–39. doi:10.1177/0269881112456611

McGovern MP, Lambert-Harris C, Gotham HJ, Claus RE, Xie H. Dual diagnosis capability in mental health and addiction treatment services: An assessment of programs across multiple state systems. Adm Policy Ment Health. 2014;41(2):205 214.doi:10.1007/s10488-012-0449-1.

Nichols, DE (2016) Psychedelics. Pharmacol Rev 68: 264–355. NIDA. 2020, June 25. Why is there comorbidity between substance use disorders and mental Illnesses? https://www.drugabuse.gov/publications/research-reports/commoncomorbidities-substance-use-disorders/why-there-comorbidity-between-substance-usedisorders-mental-illnesses.

Penson, D F, Wei, J T, Rosenberg, Andrew L, Greenfield, Marylou V H, Dimick, Justin B. Edited by: D. F. Penson and J. T. Wei. Chapter 11 / secondary data analyses from: clinical research for surgeons secondary data analyses introduction primary vs secondary datasets organization and contents and secondary datasets meta-analysis ancillary studies advantages and pitfalls how to get started examples of specific datasets conclusions references. From: Clinical research methods for surgeons / edited by David F. Penson, John T. Wei.p.; cm. 2006. ISBN 1-58829-326-2. http://eknygos.lsmuni.lt/springer/587/175-200.pdf

Psilocybin. Editor(s): J.K. Aronson. Meyler's Side Effects of Drugs (Sixteenth Edition). Elsevier. 2016. Pages 1048-1051. ISBN 9780444537164. https://doi.org/10.1016/B978-0-444 53717-1.00158-X.

Ruhé, H., Mason, N. & Schene, A. Mood is indirectly related to serotonin, norepinephrine and dopamine levels in humans: a meta-analysis of monoamine depletion studies. Mol Psychiatry 12, 331–359 (2007). https://doi.org/10.1038/sj.mp.4001949

Strasburger SE, Bhimani PM, Kaabe JH, Krysiak JT, Nanchanatt DL, Nguyen TN, Pough KA, Prince TA, Ramsey NS, Savsani KH, Scandlen L, Cavaretta MJ, Raffa RB. What is the mechanism of Ketamine's rapid-onset antidepressant effect? A concise overview of the surprisingly large number of possibilities. J Clin Pharm Ther. 2017 Apr;42(2):147-154. doi: 10.1111/jcpt.12497. Epub 2017 Jan 22. PMID: 28111761.

World Drug Report. 2020. (United Nations publication, Sales No. E.20.XI.6).

Zanos P, Gould TD. Mechanisms of ketamine action as an antidepressant. *Mol Psychiatry*. 2018;23(4):801-811. doi:10.1038/mp.2017.255

Appendix A.

MUSC Codebook

Opinions on Psychedelic Therapy

Codebook

Data Dictionary Codebook 04/20/2020 4:21pm

Collapse all instruments

	#	Variable / Field Name	Field Label *Field Note*	Field Attributes (Field Type, Validation, Choices, Calculations, etc.)
Instrument: **Pre-screener** (prescreener) Enabled as survey — Collapse				
	1	record_id	Record ID	text
	2	prescreener_use	Do you use one or more of the following substances do you use on a regular (at least once per month) basis? Alcohol Tobacco Marijuana Cocaine Opiates Amphetamines Benzodiazepines	yesno, Required 1, Yes 0, No
	3	prescreener_desirequit	Have you ever wanted to cut back on or stop using any of the above substances?	yesno, Required 1, Yes 0, No
	4	prescreener_priortx	Have you ever been in any form of treatment for alcohol or drug use?	yesno, Required 1, Yes 0, No
	5	prescreener_currenttx	Are you currently in any form of treatment for alcohol or drug use?	yesno, Required 1, Yes 0, No
	6	prescreener_complete	Section Header: *Form Status* Complete?	dropdown 0, Incomplete 1, Unverified 2, Complete
Instrument: **Opinions On Psychedelic Therapy** (opinions_on_psychedelic_therapy) Enabled as survey — Collapse				
	7	time_in	Please click now to start.	text (datetime_seconds_ymd)
	8	gender	Gender	radio, Required 1, Male 2, Female 3, Transgender or non-binary 4, Other or prefer not to answer
	9	age	Age	radio, Required 1, Under 18 2, 18 to 24 3, 25 to 34 4, 35 to 44 5, 45 to 54 6, 55+ 7, Prefer not to answer

	10	region	Region	radio 1 Northeast 2 Midwest 3 South 4 West
	11	community	Community size	radio, Required 1 Large city 2 Midsized city 3 Small city 4 Suburban 5 Rural
	12	education	Level of education completed	radio, Required 1 No high school 2 Some high school 3 High school graduate 4 Some college 5 Two-year degree 6 Completed four year college degree 7 Graduate degree training
	13	relationship	Relationship Status	radio, Required 1 Married 2 Separated 3 Divorced 4 Widowed 5 Never married 6 Domestic/civil partnership
	14	children	Do you have children under the age of 18?	yesno, Required 1 Yes 0 No
	15	race	Race/ethnicity	checkbox, Required 1 race___1 American Indian or Alaska Native 2 race___2 Asian 3 race___3 Black or African American 4 race___4 Hispanic or Latino 5 race___5 Native Hawaiian or Other Pacific Islander 6 race___6 White 7 race___7 Other or prefer not to say
	16	sud_current	Which of the following substances do you use on a regular (at least once per month) basis?	checkbox, Required 1 sud_current___1 Alcohol 2 sud_current___2 Tobacco 3 sud_current___3 Marijuana 4 sud_current___4 Cocaine 5 sud_current___5 Opiates 6 sud_current___6 Amphetamines 7 sud_current___7 Benzodiazepines 8 sud_current___8 None of the above

	17	desirequit	Have you ever wanted to cut back or quit using any of those substances?	yesno, Required 1 Yes 0 No
	18	sud_problems	Have the use of any of these substances ever caused you trouble with work, with your family or friends, or legal trouble?	yesno, Required 1 Yes 0 No
	19	psychedelic_use	Have you ever previously tried any of the following psychedelic substances? Please mark all that apply:	checkbox, Required 1 psychedelic_use___1 Psilocybin 2 psychedelic_use___2 LSD 3 psychedelic_use___3 Peyote 4 psychedelic_use___4 Ibogaine 5 psychedelic_use___5 Ayahuasca 6 psychedelic_use___6 Ketamine 7 psychedelic_use___7 Other
	20	hx_drug_tx	Have you ever been in any form of treatment for alcohol or drug use?	yesno, Required 1 Yes 0 No
	21	drug_tx_current	Are you currently in any form of treatment for alcohol or drug use?	yesno, Required 1 Yes 0 No
	22	mh_tx_hx	Have you ever received any mental health treatment?	yesno, Required 1 Yes 0 No
	23	priorunderstanding	Have you ever previously heard about the use of psychedelic-type substances (such as psilocybin, LSD, peyote, ibogaine, ayahuasca, and ketamine) being used in the treatment of addictions?	yesno, Required 1 Yes 0 No
	24	psilocybin_support	Section Header: *Psilocybin, the active ingredient in psychedelic mushrooms, has been illegal in the United States for more than 40 years. A recent study of long term tobacco smokers by researchers from Johns Hopkins showed after 2-3 treatments with psilocybin, 2/3 of study participants were able to quit smoking for over one year, and had minimal side effects. A similar, preliminary study of heavy alcohol users found that after 2 treatments of psilocybin, participants were able to reduce the number of days that they drank heavily by over ½, and were able to sustain this improvement throughout the six months that they were studied.* Do you support or oppose similar medical trials with psilocybin being conducted in the future?	dropdown, Required 1 Strongly oppose 2 Oppose 3 Neutral or unsure 4 Support 5 Strongly support
	25	psilocybin_benefits	Based on the description in the previous question and anything else you may know, Do you think psilocybin could or could not be a beneficial treatment for people suffering with addictions?	dropdown, Required 1 Strongly oppose 2 Oppose 3 Neutral or unsure 4 Support 5 Strongly support
	26	psilocybin_wouldtry	Please imagine psilocybin was proven to be safe and effective for treatment after further trials. If available to you, would you or would you not try this treatment to treat an addiction? Please select the option that best applies.	dropdown, Required 1 Definitely not 2 Probably not 3 Neutral or unsure 4 Probably would 5 Definitely would

	27	ketamine_support	Section Header: *Ketamine, a medication used for the past forty years to reduce pain when undergoing surgeries, has also been studied for the treatment of addictions. A previous study showed that after 3 treatments with ketamine in conjunction with therapy, 50% of study participants were able to be fully abstinent from heroin for over one year. A related study in heavy alcohol users found that after 1 session of ketamine in conjunction with psychotherapy, nearly 2/3 of study participants were able to maintain abstinence for over one year. Several other recent trials in cocaine users have shown that motivation to quit increases following a ketamine treatment.* Based on these findings and what you may have known before, do you support or oppose similar medical trials with ketamine being conducted in the future?	dropdown, Required 1 Strongly oppose 2 Oppose 3 Neutral or unsure 4 Support 5 Strongly support
	28	ketamine_benefits	Based on the description in the previous question and anything else you may know, Do you think ketamine could or could not be a beneficial treatment for people suffering with addictions?	dropdown, Required 1 Strongly oppose 2 Oppose 3 Neutral or unsure 4 Support 5 Strongly support
	29	ketamine_wouldtry	Please imagine ketamine was proven to be safe and effective for treatment after further trials. If available to you, would you or would you not try this treatment to treat an addiction? Please select the option that best applies.	dropdown, Required 1 Definitely not 2 Probably not 3 Unsure 4 Probably would 5 Definitely would
	30	mdma_support	Section Header: *In 2016, The FDA approved MDMA (also known as ecstasy) for Phase 3 clinical trials as a treatment for post-traumatic stress disorder (PTSD), which is a common disorder that occurs with addictions. These Phase 3 trials are one of the final steps before possible approval as a prescription drug. One study showed that with 3 doses of MDMA administered under a psychiatrist's guidance, the patients reported a 56% decrease of severity of symptoms on average. At the end of the study, 66% no longer met the criteria for having PTSD — improvements lasted more than a year after therapy.* Based on these findings and what you may have known previously, do you support or oppose similar medical trials with MDMA being conducted in the future?	dropdown, Required 1 Strongly oppose 2 Oppose 3 Neutral or unsure 4 Support 5 Strongly support
	31	psychdelics_concerns	Do you have any of the following concerns about using psychedelics (psilocybin, ketamine, MDMA, or other psychedelic medications) to reduce or stop using alcohol or other drugs? Please mark all that apply.	checkbox, Required 1 psychdelics_concerns___1 Fear of a bad trip 2 psychdelics_concerns___2 Fear that you wouldn't enjoy using your substance of choice as much afterwards 3 psychdelics_concerns___3 Fear that it would "change you" 4 psychdelics_concerns___4 Fear that it would cause you to "go crazy" or "lose your mind" 5 psychdelics_concerns___5 Fear that you would harm yourself or others while on a bad trip 6 psychdelics_concerns___6 Fear that you would feel guilt during your trip 7 psychdelics_concerns___7 Fear that you would lose your sense of self 8 psychdelics_concerns___8 Fear that it would affect your employment

				9	psychdelics_concerns___9	Fear that your family, neighbors, or others in the community would have a negative opinion if they found out that you have an addiction or trouble controlling your use of substances
				10	psychdelics_concerns___10	Fear that your family, neighbors, or others in the community would have a negative opinion if they found out that you used this for treatment
				11	psychdelics_concerns___11	Belief that the treatment would be too expensive
				12	psychdelics_concerns___12	Feeling like you are not ready to stop drinking alcohol or using drugs
				13	psychdelics_concerns___13	Feeling like life would be boring or not worth living if you stopped drinking alcohol or using drugs
				14	psychdelics_concerns___14	Have concerns other than those listed above
				15	psychdelics_concerns___15	No concerns
	32	psychedelics_interest	Which of the following would you be interested in trying as a treatment to reduce or quit using alcohol or drugs? Please mark all that apply.	checkbox, Required		
				1	psychedelics_interest___1	Psilocybin
				2	psychedelics_interest___2	LSD
				3	psychedelics_interest___3	Peyote
				4	psychedelics_interest___4	Ibogaine
				5	psychedelics_interest___5	Ayahuasca
				6	psychedelics_interest___6	Ketamine
				7	psychedelics_interest___7	MDMA
				8	psychedelics_interest___8	Not interested in trying any of these
	33	psychedelics_concern	Which of the following would you be concerned about trying as a treatment to reduce or quit using alcohol or drugs? Please mark all that apply.	checkbox, Required		
				1	psychedelics_concern___1	Psilocybin
				2	psychedelics_concern___2	LSD
				3	psychedelics_concern___3	Peyote
				4	psychedelics_concern___4	Ibogaine
				5	psychedelics_concern___5	Ayahuasca
				6	psychedelics_concern___6	Ketamine
				7	psychedelics_concern___7	MDMA
				8	psychedelics_concern___8	No concerns about any of these

	34	compensation	Would you like to receive compensation for completing the survey? If so, you must be willing to provide your email address.	yesno, Required 1 Yes 0 No
	35	time_out	Please click now when you have completed the survey.	text (datetime_seconds_ymd), Required
	36	total_time	Total time	calc Calculation: datediff([time_in], [time_out], "m") Field Annotation: @HIDDEN-SURVEY
	37	opinions_on_psychedelic_therapy_complete	Section Header: *Form Status* Complete?	dropdown 0 Incomplete 1 Unverified 2 Complete
Instrument: **Email** (email) Enabled as survey				Collapse
	38	email	Please provide your email address to receive compensation via an Amazon giftcard.	text (email), Required
	39	email_complete	Section Header: *Form Status* Complete?	dropdown 0 Incomplete 1 Unverified 2 Complete