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Article

The Psychiatric Utility of MDMA

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Objective: This paper aims to compile the history, available data, pharmacology, and notable studies of 3,4-Methylenedioxymethamphetamine (MDMA), more commonly referred to as ecstasy, order to assess any potential medical utility.
Methods: Literature Review
Discussion: MDMA, when combined with appropriate psychotherapy, appears to have a statistically significant and rather large effect on the reduction of PTSD symptoms. It has also been investigated for use in alcohol use disorder, autism spectrum disorder, and social anxiety disorder. Phase III clinical trials are underway, and MDMA assisted psychotherapy could be and FDA approved treatment for PTSD as early as 2021. Caution must be used to ensure there are no significant risks including addiction or long-term side effects from use, but early clinical trials suggest a reasonable safety profile.

Introduction

Generally referred to as "ecstasy," 3,4-methylenedioxymethamphetamine (MDMA) has been a popular drug used for recreational purposes since the 1960s and has been investigated for potential psychiatric utility in the treatment of several disorders. Other street names include Adam, "molly," XTC, E, X, MDM, and EA-1475. MDMA is a highly polarizing agent within the general public and medical community and has an extensive list of potential benefits and adverse effects. It has garnered attention for its potential use in helping patients suffering from symptoms of PTSD and other psychiatric disorders.

History

German chemist Anton Kolisch first synthesized MDMA for the pharmaceutical company, Merck, in 1912 [8,9]. Much like the discovery of lysergic acid diethylamide (LSD) in 1943, MDMA was discovered accidentally during efforts to synthesize a new hemostatic agent [7]. MDMA was initially classified as an intermediate compound in the process of synthesizing methylhydrastinine, and Merck had no apparent interest in the compound at that time [5,8]. There was no record or mention of MDMA by the company until 1927 when another chemist studying adrenaline and ephedrine noted the structural similarity of MDMA to these compounds. Some initial studies were undertaken, which concluded that the compound did not have 'pure sympathetic effects.' The next records of MDMA from Merck were not until 1952 [8]. The predominant research at that time appears to have been looking into the toxicology of the compound. In the 1950s, the United States Army at the University of Michigan began studying MDMA for toxicology purposes. There is no evidence of human testing of MDMA until at least 1960 [8,9].

By the 1960s, while little was known about MDMA, word had gotten out about the desirable effects. In 1970, before any legitimate human studies, law enforcement seized MDMA tablets from the streets of Chicago [8,11]. American chemist Alexander Shulgin was next to advance the knowledge of MDMA. Well known for his interest in psychoactive compounds and prior to his work with MDMA, Shulgin had focused on the similar compounds 3,4-Methylenedioxyamphetamine (MDA) and 3-methoxy-4,5-methylenedioxyamphetamine; 5-methoxy-MDA (MMDA). While working at San Francisco State University in the 1970s, various colleagues had spoken to him about the effects of the drug, attracting his interest. In 1978, Shulgin, along with medicinal chemist David Nichols published a paper discussing the effects of MDMA in humans.

In this paper, the psychotomimetic properties of the drug were described as follows: "Qualitatively, the drug appears to evoke an easily controlled altered state of consciousness with emotional and sensual overtones. It can be compared in its effect to marijuana, to psilocybin devoid of the hallucinatory component, or to low levels of MDA [12]." At the time, MDA was a structurally similar, better known, schedule 1 drug that produced euphoric and stimulating effects, but was never as popular as MDMA. In 1986 and 1990, Shulgin published two more papers discussing MDMA and even suggesting that it may have utility as an adjunct to psychotherapy due to its observed effects of disinhibiting the patient [9,10].

In addition, to his research contributions, Alexander Shulgin is thought to have introduced MDMA to Leo Zeff in 1977 [9]. Dr. Zeff was an American psychologist and psychotherapist who had been using LSD in his practice since 1961 and gained notoriety for famously nick naming MDMA "Adam" as he thought that it returned the user to a "primordial state of innocence [9]." There is limited data discussing the specific psychotherapeutic techniques that Dr. Zeff employed, but he is well known as an early advocate for the use of MDMA and encouraged its use amongst his colleagues [9,10].

MDMA was introduced as a street drug at some point in the 1960s [5,8]. Most of the production was thought to have been from underground chemists, and the purity was inconsistent. MDMA was initially thought of as a legal alternative to MDA, which had been scheduled as a controlled substance in 1970. The drug initially surfaced in the Midwest, and until 1974 nearly all street samples of the drug were confiscated with the first recorded seizure in Chicago in 1970. MDMA was first detected in Canada in 1974 and was quickly scheduled as a controlled substance in 1976 [5]. From 1975-1980 the use of MDMA became more localized to the West Coast with street samples being found in multiple other states [8,11].

In the 1980s, psychotherapists using MDMA attempted to keep the drug in the clinical research community to avoid the repercussions that would follow if the drug were to become diffusely popular. However, by this time, MDMA had been used on the streets for years, and in the early 1980s, MDMA was rebranded as "Ecstasy [3,8,9]." Its use became popular, especially at parties or "raves." In 1984 the DEA finally moved to ban the compound due to rising seizures of the drug by police and concerns over increasing use nationwide. Despite the clinical MDMA research community's attempt to stop the drug from being banned, in 1985, MDMA was placed in emergency Schedule One classification, and from that point forward, its status as a scheduled drug has become permanent. As expected, since 1985, research into MDMA became profoundly difficult. Compared to Europe, the use of MDMA in the USA in the 1980s was relatively limited; in Europe, it was a popular recreational drug during this time. Recreational use of MDMA began to rise significantly in the mid-1990s in the USA [11].

Pharmacology

MDMA is structurally similar to amphetamines and certain hallucinogens such as mescaline [5]. Despite its relatively simple chemical structure, MDMA manages to have a vast range of effects on receptors, neurotransmitters, and hormone release. MDMA's most notable effects are on monoamines such as serotonin, dopamine, and norepinephrine through multiple mechanisms; the main effect of acute MDMA exposure is increased extracellular serotonin concentration. MDMA is known to inhibit serotonin transporter (SERT), dopamine transporter (DAT) and norepinephrine trans-

porter (NET), which leads to impaired reuptake and increased extracellular levels of the monoamines [5,13]. This is thought to be due to competitive inhibition, as MDMA acts as a substrate for these transporters. MDMA is a more potent inhibitor of SERT than DAT or NET leading to a comparatively greater increase in the concentration of extracellular serotonin Once inside, a monoamine neuron MDMA binds to and inhibits vesicular monoamine transporters (VMAT) and, more specifically, vesicular monoamine transporter 2 (VMAT2). The purpose of VMAT2 is generally to transport monoamines from cellular cytosol into synaptic vessels. This inhibition results in an increased concentration of dopamine, serotonin, and norepinephrine in the cellular cytosol [5,13,14]. MDMA then leads to direct release of serotonin, dopamine, and norepinephrine into the extracellular space by reversing the direction of the flow of the monoamines through their native transporters at the cellular membrane once intracellular concentrations of the monoamines rise to a significant enough level to create a concentration gradient [26]. The releasing effects of this method are increased in serotonin and norepinephrine compared to dopamine [5].

MDMA is also known to bind directly to several important neuroreceptors, although for the most part, it binds to them weakly suggesting its activity at VMAT2 and the monoamine transporter inhibition is more important [5,13]. These receptors include H1 histaminergic, B-adrenergic, serotonergic, dopaminergic, and muscarinic receptors. The most robust serotonergic activity on a receptor is on the 5-HT2B receptor as an agonist, although this currently has unclear significance. MDMA is also active at the trace-amine associated receptor (TAAR1), where it acts as an agonist. TAAR1 has many functions, including regulating neurotransmission in dopamine, serotonin, and norepinephrine neurons in the central nervous system. Activation of TAAR1 by MDMA leads to protein kinase A and protein kinase C activity, which leads to the phosphorylation of the monoamine transporters DAT, SERT, NET in the neuron [5,13]. This leads to either reversal in the direction of transport systems, moving cytosol neurotransmitters to the synaptic cleft, or withdrawal of transporters back into the cell functionally leading to inhibition. These actions increase the extracellular concentrations of serotonin, dopamine and norepinephrine. It has also been shown that MDMA binds to the sigma-1 and sigma-2 receptors. The exact role of these receptors is unknown, but other psychoactive drugs bind to it, including phencyclidine (PCP), methamphetamine, and dextromethorphan, among others [5]. The sigma-1 receptor has gotten some interest as being a potential target for antidepressant and anxiolytic medication as some current psychiatric medications act as agonists at the receptor, including citalopram and fluvoxamine [5,14].

MDMA is known to have hormonal effects leading to increases in the plasma concentrations of cortisol, prolactin, dehydroepiandrosterone (DHEA), vasopressin, and oxytocin [5]. Oxytocin is of specific interest due to the role it is thought to have in prosocial feelings. In a study by Dumont et al. published in 2009, they showed that increases in oxytocin in blood levels correlated more closely than concentrations of MDMA in the context of increasing prosocial behavior [15]. Other studies have not demonstrated this relationship but have confirmed an increase in oxytocin. The behavioral effects of this hormone on the user of the substance are still unclear.

PTSD Research

Psychedelics have been explored as potential adjuncts to psychotherapy since the early 1900s, including psilocybin, LSD, and MDMA [3,7]. MDMA has garnered particular attention as an agent to help treat post-

traumatic stress disorder (PTSD) due to the potential to temporarily decrease the fear response during a therapy session while increasing trust and empathy in the therapeutic relationship [1,2,4]. In the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V), a diagnosis of PTSD requires exposure to an actual or threatened death, serious injury or sexual violence which could be experienced in several different ways including directly experiencing or witnessing a traumatic event, learning about a close friend or family member's traumatic experience or repeated or extreme exposure to aversive details of a traumatic event. The core symptoms of PTSD include intrusive symptoms such as nightmares or flashbacks related to the incident, avoidant behavior, negative mood, and alterations in arousal leading to hypervigilance, sleep disturbance, concentration deficit, or increased startle response [2,17]. It is difficult to estimate the prevalence of PTSD, but the World Health Organization World Mental Health (WMH) Survey analysis examining data from 26 different countries, and a total of 71,083 respondents estimated the lifetime prevalence of PTSD to be about 3.9% globally. These surveys were completed between 2001-2012 [16]. PTSD takes a significant toll on the well-being of individuals along with a large but difficult to estimate economic cost through lost productivity and treatment.

Current guidelines in the treatment of PTSD recommend the use of psychotherapy as first-line treatment over current pharmacological options. The specific therapies used are exposure therapy and trauma focused cognitive behavioral therapy (TF-CBT). There are only two medications that are FDA approved to treat PTSD currently: sertraline and paroxetine. In clinical practice, more medications are used to treat PTSD, including other selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), atypical antipsychotics, benzodiazepines, and many other medications [17]. Therapy is always recommended, but not always available and not everyone will respond to treatment with medication or therapy.

Due to the scheduling of MDMA in 1985 there were no clinical trials of the substance until the year 2000. In 1986 the Multidisciplinary Association for Psychedelic Studies (MAPS) filed a Drug Master File application and then in 2001 an Investigational New Drug (IND) application. This allowed the MAPS to work within FDA guidelines to study the safety and efficacy of MDMA as an adjunct to psychotherapy for PTSD [19]. MDMA is thought to be an excellent drug to use in concert with psychotherapy due to positive effects on trust and empathy, along with the limited perceptual disturbance and generally retained cognitive function [2]. Six MAPS-sponsored randomized, double-blind phase two studies will be discussed, that took place between 2004-2017, although there have been general tolerability and case studies that showed promise as well [25]. In 2017, after reviewing the data in 2016, the FDA granted a Breakthrough Therapy Designation to MDMA and approved two phase III trials, which started in 2018 but do not yet have published results [19].

The first randomized controlled pilot study was done by Mithoefer et al. with enrollment from 2004-2008 and follow up being completed in 2008 [18]. Candidates for the study were required to have Chronic PTSD with symptoms lasting over six months, along with the Clinician-Administered PTSD Scale for DSM-IV (CAPS-IV) scores ≥ 50. This was also true of the other 5 MAPS sponsored phase II studies except for one study requiring a score of ≥ 60 in Canada [18,19]. Subjects included men and women, both civilians and veterans, and they

must have been at least age 18 years old. It was required that they had failed one previous pharmacotherapy or psychotherapy to treat PTSD which they counted as an inadequate response to previous treatment; the average amount of medications failed for this initial study was 4.2 psychiatric medications with at least one unsuccessful course of psychotherapy in 75% of the patients in the study. Participants were not excluded for meeting criteria for anxiety or depressive disorders but were excluded if they met the criteria for a psychotic disorder, bipolar disorder, eating disorders, or borderline personality disorder. The other exclusion criteria included significant medical diagnoses that could be exacerbated by MDMA, pregnancy, or weight under 48 kilograms. Those with substance use disorders were excluded if the diagnosis was active within 60 days of screening [18,19].

In this first study done by Mithoefer et al. of the group of six phase II clinical trials coordinated by MAPS, 20 patients underwent the study after two patients ended up dropping out due to relapse of depression and inability to travel for the study. The subjects were randomized into two groups in a double-blind fashion to receive two experimental psychotherapy sessions with MDMA administration (12 patients) or with placebo (8 patients). Patients were required to taper off of all psychotropic medications prior to the study, and the only psychotropic medications used in concert with the MDMA or placebo were as needed zolpidem or lorazepam generally for insomnia treatment [18].

No greater than six weeks before the first experimental sessions, each subject underwent two 90 minute introductory sessions helping them become familiar with the experimental protocol. A male and female co-therapist team of a psychiatrist and psychiatric nurse were present for all therapy sessions in the study, and the same team was used each time for a given patient. They had been trained in MAPS Therapy Training Program based on the method described in the MDMA-assisted Psychotherapy Treatment Manual, so there was consistency between sessions. In addition to the experimental sessions, there were non-drug therapy sessions for both the treatment and control groups. In total, outside of the introductory sessions, there were two experimental sessions, where administration of drug or placebo occurred, along with a standard eight integration sessions focusing on experimental sessions and additional emotional processing. There was some variation in time elapsed between sessions, but all non-drug psychotherapy sessions occurred 1-7 days apart and 3-7 days after the experimental sessions [18,19].

Experimental sessions took place in a comfortable, aesthetically pleasing environment with a sofa capable of reclining, with the co-therapists sitting on both sides of the patient in chairs. In this first study with Mithoefer et al., the dosage of MDMA was selected to be 125mg, and the placebo was simply lactose. MDMA or placebo was given at 10 am, and the sessions lasted 8-10 hours with a required overnight stay the night of the experimental session. The subject would either have their eyes closed or would wear eyeshades as music played. This music was designed to be initially relaxing and then transition to emotionally evocative; the music was identical for each subject, but they did have the power to skip over songs and replace them with silence instead. The co-therapists would help guide patients through the experience with a therapeutic conversation and the encouragement of introspection, the proportions of each was based on the patient response and clinical judgment of the therapists. An optional supplemental dose of 62.5mg of MDMA was offered 2-2.5 hours after administering the initial dose if deemed safe and appropriate, which was accepted in

22 of the 23 sessions in which it was an option. There was also a cross-over section of the study, which was open-label, and thus the data is excluded in the final results; however, it is essential to note this arm of the study for long-term follow-up purposes. This cross-over arm of the study only included those in the placebo group who were not exposed to MDMA and was not offered until after the two-month follow-up data was acquired, which was the endpoint of the initial study. Functionally, it means that 19/20 of the subjects eventually ended up being exposed to MDMA [18].

The onset of effects in those patients treated with MDMA was generally between 45-75 minutes after ingestion [18,19]. Peak effects occurred 2-2.5 hours after the initial dose and lasted between 4-5 hours and 5-6 hours in those that received the supplemental dose after 2-2.5 hours as above. This study demonstrated statistically significant increases in blood pressure, heart rate, and temperature when comparing pre-session to highest recorded during session values. However, there was no significant difference between the groups in vital sign measurement at the completion of the session measured at 6 hours after ingestion. Side effects reported by patients were more common in the MDMA group versus the placebo group, included nausea, dizziness, loss of appetite, impaired balance, feeling cold, and jaw tightness. On the treatment day, the placebo group had higher rates of anxiety and insomnia with comparable rates of headaches and fatigue. The most striking of these effects were jaw tightness with 79% of those in the MDMA group experiencing it versus only 19% of placebo; nausea with 50% in the MDMA group versus 13% in placebo, and impaired balance with 25% experiencing it in the MDMA group versus 0% in the placebo group. They also discussed side effects experienced at some point in the seven days after the treatment with generally similar rates of side effects except for an increase in irritability and loss of appetite in the MDMA group and insomnia in the placebo group. Side effects generally resolved on their own, but some patients were given sedative-hypnotics or non-steroidal anti-inflammatory drugs following experimental sessions [18].

The primary outcome of the study was the reduction in CAPS-IV scores. Patients' scores were compared from less than four weeks before the first treatment with placebo versus MDMA (79.6 vs 79.2; p-value of 0.966), 3-5 days after the initial treatment (74.1 vs. 37.8; p-value of 0.013), 3-5 days after the second treatment (66.8 vs. 29.3, p-value of 0.002) and two months after the second treatment (59.1 vs. 25.5, p-value of 0.013). The PTSD symptoms, as measured by CAPS-IV, improved over time in both groups but the MDMA group showed a significantly greater improvement in symptoms compared to placebo as can be seen above. In order to correct for multiplicity, Mithoefer et al. examined mean differences between 'group × time' using independent *t*-tests with Holm's sequential Bonferroni correction (α). The reductions in CAPS-IV scores were found to be significant in all groups except the initial group prior to initiation of treatment as above. PTSD symptoms measure by Impact of Event Scale-Revised (IES-R), another PTSD rating scale but not the primary outcome of the study, followed a similar pattern of comparable improvement in symptoms. Clinical response was defined as >30% reduction from baseline in CAPS total severity score with 83.3% (10/12) in the MDMA group versus 25% (2/8) in the placebo group showing this improvement. Of note, there was no significant difference in scores between patients who received the supplemental dose versus those who did not. In order to try to evaluate for potential cognitive function change a battery of tests were performed prior to the first dosing of

MDMA and two months after the second dosing including the repeatable battery for the assessment of neuropsychological status (RBANS), Paced Auditory Serial Addition Test (PASAT) Trial 1 and 2, and the Rey-Osterrieth Figure 30-minute delay. At baseline, there were no significant differences between the MDMA or placebo receiving groups. Comparing the two groups at the two month follow up there again were no differences in any of the significant index scores [18].

After the completion of this study Mithoefer et al. attempted to investigate the durability of improvement in PTSD symptoms and published a follow-up paper in 2013 [20]. Due to the cross-over arm of the initial study, 19/20 of the initial patients ended up receiving MDMA. Due to a protocol amendment from the first study, eight subjects received three MDMA sessions, and 11 subjects received two MDMA sessions prior to long term follow up (LTFU) participation. All 19 of these initial subjects participated in the LTFU, with 16 of the 19 completing all outcome measures. The CAPS score was the primary outcome measure with the IES-R again being used along with a questionnaire designed to get information about various things including the perceived benefits or harms from the study. The LTFU questionnaire and questionnaire were mailed to the patients, and the CAPS was done over the phone or in-person by the same rater that had initially done the individual patient's CAPS. This investigation was conducted 17 to 74 months after completion of the final MDMA session with an average of 3.5 years per patient. At LTFU, 13% (2/19) of the patients had CAPS scores > 50, indicating relapse of PTSD with moderate to severe symptoms. When the three patients who did not complete the CAPS at LTFU are added, constituting intent-to-treat analysis, the number is 26% (5/19). The mean CAPS and IES-R scores at LTFU were not statistically different when compared to the two month mean scores indicating long term improvement in symptoms. While the questionnaire sent out was not a validated instrument, it did provide interesting information. No one felt that they were harmed by participation in the study. There was no change in substance abuse habits before versus after the initial study as patients had already informed the investigators of their substance use before the first study, the most common substance was recreational cannabis use with eight patients reporting intermittent use. Of note, one patient stated that he had again used MDMA prior to the completion of the LTFU in a semi-therapeutic setting to replicate the strategy used in the initial study. He had a friend be present during the study; however, he did not find this beneficial and reported no plans for further use of MDMA. All participants in the survey did state that they felt further sessions of MDMA, and psychotherapy would be helpful, either "at a later time point" or "soon after the first one." Overall, no lasting adverse medical or psychiatric effects were observed [20].

After the first study by Mithoefer et al., a group in New Zealand, Oehen et al. attempted to replicate the promising results from the initial study [21]. Patients were enrolled from 2006-2009 with follow up completed in 2011. The study inclusion criteria and design were essentially the same as those done by Mithoefer et al. with a significant difference in the control group. Instead of using an inactive placebo, low dose MDMA was used with 25mg given in the initial dose plus a possible 12.5mg supplemental dose. The full dose was again 125mg with a 62.5mg supplemental dose. This was done to try and address the difficulty with successfully double-blinding a powerful drug like MDMA to allow for the low dose group to experience detectable but likely sub-therapeutic effects. The sample

size was 12 with eight patients randomly assigned to the full-dose group and four to the lower dose group. There were three planned experimental sessions and CAPS scores were acquired at baseline prior to treatment, three weeks after MDMA session #2, 3 weeks after MDMA session #3 (the end of treatment), along with 2, 6 and 12 months after MDMA session #3.

Interestingly, in this study with the lower dose MDMA "active placebo" group, the CAPS scores increased slightly from baseline (63.5) versus three weeks after the study (66.5). Over the same period, the full-dose group's CAPS scores went from baseline (66.4) versus three weeks after the study (50.8) This constituted an average drop of 16.2 points or 23.5%. While this did show a decrease in CAPS score compared to the active placebo group, the difference was found to not be statistically significant with a p-value of 0.066. This study did show that the overall tolerability of MDMA was favorable in a clinical setting with no significant adverse events. It is unclear why this study did not show a statistically significant difference between the groups, but the authors suggested it could be related to cultural differences, the smaller sample size in general, or due to the higher overall CAPS scores at baseline of the Mithoefer et al. study [21].

As discussed above, this study by Mithoefer et al. was the first of six randomized, double-blind, controlled clinical trials at five study sites sponsored by MAPS. The studies all had similar designs allowing producing more consistent results. Some differences between the studies included the dosing of MDMA used in the treatment group and if they used a true placebo or active placebo as done by Oehen et al. Doses for the treatment group in these studies ranged from 75 mg, 100 mg, or 125 mg and placebo 0 mg, 25 mg, 30 mg, or 40 mg respectively. The data from the above Mithoefer et al. study is included in the final analysis of the MAPS trials [19,22]. Between the six studies, there were 105 patients: 31 in the control group and 74 in the active group. The baseline CAPS-IV scores were 85.8 for the treatment group and 81.3 for the control group indicating severe PTSD symptoms with slightly higher scores noted in the treatment group. Change in CAPS scores from baseline was significantly different between the groups with an estimated change in the active group of -30.4 and -10.5 in the placebo group with a p-value of < 0.0001. The percentage of patients no longer meeting criteria for PTSD after the second treatment for the active group was 54.2%, and for the control was 22.6%. The between-group effect size was large and calculated to be 0.8 using Cohen's *d*. A secondary outcome used in four of the six clinical trials was a reduction in The Beck Depression Inventory-II (BDI-II). The change in scores from baseline after the second treatment was -12.4 for the active group and -6.5 for the control; the difference between the groups did not quite meet statistical significance with a p-value of 0.053[19].

Throughout these clinical trials, there were four serious adverse events with three of them considered to be unrelated to treatment including suicidal ideation in a patient receiving active control in the context of a life stressor, suicidal behavior in a patient prior to the first treatment session, along with another patient developing appendicitis. The final serious adverse event was an exacerbation of pre-existing premature ventricular contraction in a patient after receiving 125mg of MDMA; the patient did recover without permanent issues but required overnight cardiac monitoring. During the treatment sessions, the most common adverse events experienced between the treatment and control groups were: anxiety (72% active vs. 48% control), jaw clenching (64% vs. 19%), dizziness (40% vs. 19%), nausea (40% vs. 19%) and loss of

appetite (49% vs. 23%). A transient elevation in vital signs was again noted, which resolved spontaneously after the experimental sessions [19].

As noted earlier, the results of these clinical trials were so encouraging that the MAPS group moved forward with phase III clinical trials, which are currently underway [19,22]. The reduction in PTSD symptoms when using MDMA assisted psychotherapy is impressive, especially when combined with the potential for long-lasting remission, as noted by Mithoefer et al. in their follow up study on average 3.5 years after completion of this treatment [20]. Overall, the use of MDMA when carefully monitored by medical professionals appears to be safe; however, further attention may need to be paid to patients with existing arrhythmias or other cardiac conditions. It is still unclear what the optimal dose of MDMA is as reasonable results were produced with doses of 75mg, 100mg, and 125mg; this will be investigated further in phase III clinical trials [19]. Due to the common use of MDMA recreationally, there are warranted concerns for drug abuse or misuse associated with using MDMA as a therapeutic treatment. At this point, MDMA, when combined with psychotherapy, appears to have a low potential for abuse. There were no adverse events related to MDMA seeking behavior or craving of the substance noted during the studies. In the follow-up study by Mithoefer et al., it was noted that one patient attempted to replicate the clinical trial conditions in their personal life and did use MDMA. This type of behavior will need to be monitored closely, going forward. A barrier to the widespread use of this method is the likely cost that will be associated with the psychotherapy and close monitoring of patients during and after administration of MDMA. While MDMA assisted psychotherapy will likely not become a first-line treatment for PTSD immediately, it does have clear potential to help certain patients who have failed other treatments. If the results of phase III clinical trials are equally positive, MDMA assisted psychotherapy could be an FDA approved treatment option for PTSD as early as 2021 [19,22].

Alcohol Use Disorder

While MDMA has not received as much attention as a possible treatment for certain addictions, compared to other psychedelic medications such as LSD or psilocybin, it has been postulated that it could be a potential treatment option for alcohol use disorder (AUD) [31]. The key features of AUD, according to DSM-V, include general life dysfunction related to alcohol use, difficulty cutting down on use, drinking more than intended, continued use in dangerous situations, and symptoms of tolerance and withdrawal. The economic and societal burden exerted by AUD is significant with a twelve-month and lifetime estimation of prevalence in the United States of 13.9% and 29.1%, respectively. Compared to the research on MDMA assisted psychotherapy for PTSD, there is a paucity of data investigating if this strategy could be effective for AUD [24].

To date, there is only one published study related to MDMA assisted psychotherapy as a treatment for AUD done by Sessa et al. It is an open-label safety and tolerability proof of concept study and is still ongoing, but they have presented preliminary data [23]. Subjects were adults with diagnosed AUD who had successfully undergone community alcohol detoxification. For the most part, the study design and exclusion criteria mimic what was used to investigate MDMA assisted psychotherapy for PTSD treatment. Subjects underwent an 8-week course of MDMA assisted psychotherapy with a total of 10 sessions utilizing motivational enhancement therapy. MDMA

was administered at sessions in weeks 3 and 6 at doses of 125mg with an optional 62.5mg booster dose 2 hours after. So far, Sessa et al. have released data about four patients who have completed this constituting a case series. They did not present data from a standardized rating scale such as the Alcohol Use Disorders Identification Test (AUDIT), but their primary outcome measured was drinking habits. The authors acknowledge that they are not reporting detailed outcome data concerning drinking patterns as the study is ongoing. Of the four patients followed for nine months after this treatment, two reported complete abstinence, and two reported single episodes of small amounts of alcohol use; none returned to daily or harmful drinking. No adverse events were noted during the study, and similar physiologic responses compared to similar studies were shown. The treatment appears to be well-tolerated, and the authors have discussed undertaking a future randomized placebo-controlled study [23].

Autism Spectrum Disorder and Social Anxiety

Autism spectrum disorder (ASD) is characterized by deficits in social communication and the presence of restricted interests and repetitive behaviors. It is a neurodevelopmental disorder influenced by both genetic and environmental factors, but no clear unifying cause has been identified. The World Health Organization (WHO) estimates that the international prevalence of ASD is 0.76% while in the United States, a parent-reported survey averaged about 2.5% in 2014 [29]. In 2013 epidemiological data were collected from patients with ASD who were either MDMA experienced or MDMA naïve. After reviewing feedback from patients and formal assessment tools, it was hypothesized that MDMA could be helpful in the treatment of ASD who suffer from social anxiety disorder (SAD) [30]. SAD is generally characterized as intense fear or anxiety related to social situations leading to some degree of impaired ability to function. People with ASD are thought to be at greater risk of developing SAD [29].

Between 2014-2017 a randomized, placebo-controlled, double-blind study was undertaken to investigate if MDMA could have utility in treating SAD in patients with ASD [28]. A total of 12 participants were recruited and randomized to receive either placebo (four patients) or MDMA (eight patients) groups, and both received the same psychotherapy. To be eligible the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition Axis I Research Version (SCID-I-RV) and Autism Diagnostic Observation Schedule (ADOS-2 Module 4) to confirm ASD diagnosis and a Leibowitz Social Anxiety Scale (LSAS) score of 60 or higher was required indicating diagnosis of SAD. Participants were at least 21 years of age and had never tried MDMA by self-report. The subjects were not required to have treatment-resistant SAD, but 8/12 (66.7%) had tried some sort of psychotropic medication in the past, and 10/12 (83.3%) had tried psychodynamic psychotherapy. The design and exclusion criteria were generally similar to the design used in the PTSD studies unless otherwise noted. There were three preparatory psychotherapy sessions before the experimental session, where patients were given MDMA or placebo. Three more sessions of integrative psychotherapy occurred over the following three weeks, followed by another experimental session one month after the first session. After three more psychotherapy sessions over three weeks, the study was completed [28].

During the preparatory psychotherapy sessions, the structure of the study was discussed with the patients, and rapport was established. Mindfulness therapy ad-

apted from dialectical behavioral therapy (DBT) was used in subsequent sessions to help support patients struggling with interpersonal relationships, emotional regulation, and distress tolerance. During the experimental sessions, patients were closely monitored and supervised similarly to the studies looking into PTSD. Four of the patients in the active group were to be given 75mg of MDMA in the first session and 100mg in the second, the other four were to be given 100mg of MDMA in the first session and 125mg in the second; however, for statistical analysis, all patients receiving MDMA were grouped together. The control was a true placebo in the form of lactose [28].

The primary outcome of the study was the mean change in LSAS scores from baseline comparing the active to the control group. An independent rater administered the LSAS at baseline, 1 day, 2 weeks, and 4 weeks after each experimental session and then again at six months after completion of the study; the same rater was used for the entire study. The study's primary endpoint was the change in LSAS score from baseline to 4 weeks after the second experimental session. Mean LSAS scores at baseline were 91.8 for the MDMA group and 83.3 for the control group, which improved to 46.4 for the MDMA group and 64.0 for the control group at four weeks after the second experimental session. The mean change in LSAS scores from baseline to the primary endpoint of -44.1 for the MDMA group and -19.1 for the control group constituted a significant difference in LSAS scores between the groups with a p-value of 0.036. The placebo-subtracted Cohen's *d* effect size was 1.1, which indicates a large effect size. At the six-month follow-up the change in LSAS scores from baseline remained essentially the same when compared to the change in scores from the primary endpoint with -47.7 for the MDMA group and -23.3 for the control group. Of note, one patient in the active group dropped out of the study for unclear reasons and is counted as a treatment failure. The rate of clinically significant changes in SAD symptoms from baseline was 6/8 (75%) with MDMA versus 2/4 (50%) with placebo with significant change defined as a change in LSAS score of 20 or more points [28].

No significant adverse events were reported in the study with the most common adverse events occurring in the experimental session in the MDMA versus placebo group being anxiety (75% in the MDMA vs. 25% placebo), difficulty concentrating (62.5% MDMA vs. 25% placebo), along with more frequent headache, fatigue, and sensitivity to cold in the MDMA group. A severe headache was reported. Other symptoms were similar between the groups, including 25% of patients experiencing suicidal ideation in both groups, but this was pre-existing in the medical history [28].

Although the sample size was small, the results were encouraging and warrant further investigation. Similar to the results from the PTSD studies, there is hope that treatment with MDMA and psychotherapy could lead to long term improvement in symptoms in patients with ASD who suffer from SAD.

Discussion

Recently, psychedelic compounds have been investigated as treatments several psychiatric disorders, with Ketamine already being an FDA approved treatment for treatment-resistant depression. LSD, psilocybin, and especially MDMA appear to have garnered plenty of excitement as well [17]. MDMA has primarily been investigated for use in patients with PTSD. MDMA or placebo was combined with standardized, trauma-focused therapy and administered in a controlled environment in these studies. MDMA, when combined with appropriate psychotherapy, appears to have a statistically significant and

rather large effect on the reduction of PTSD symptoms. These results have been so promising that phase III clinical trials are currently underway and if these are also positive MDMA assisted psychotherapy could be an FDA approved treatment option for PTSD as early as 2021 [19,22]. MDMA-assisted psychotherapy has also shown promising results for the treatment of alcohol use disorder, and autism spectrum disorder with social anxiety. As with all controlled substances, the risk for addiction needs to continue to be investigated, but thus far, the risk appears to be minimal when used in a controlled environment by medical professionals. There is also a lack of long-term data about the potential adverse effects of using MDMA, but it appears to be surprisingly well tolerated. Both addiction risk and long-term side effect risks will be studied more thoroughly during phase III clinical trials for PTSD. It is easy to be excited about the potential use of MDMA for treating PTSD and perhaps other psychiatric disorders. We must continue to review the research to make educated treatment recommendations for our patients going forward as more psychedelic treatments become available for clinical use.

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Life After Attempted Death: A Case Report of Symptom Mitigation with the Use of LSD in Methamphetamine Use Disorder and Other Psychiatric Comorbidities

JP Martell, M.D.

Abstract:
The Use of psychedelics, such as LSD, in the treatment of psychiatric conditions, remains controversial. Early LSD studies showed positive results in the treatment of psychiatric disorders, but critics point to questionable methodologies and poor data analysis as an alternative explanation for these results. As a result of the society backlash against psychedelics, LSD was included in the Convention of Psychotropic Substances of 1971 as a schedule 1 substance, further limiting its inclusions in research efforts. More recent interest in the use of psychedelics as potential treatments for psychiatric conditions including substance, mood trauma, and anxiety related disorders, will prompt researches towards exploring new, and promising avenues in neuroscience. Additional research into the therapeutic uses of LSD is necessary to determine its role in the treatment of psychiatric and substance use disorders.

Introduction

After cannabis, stimulants constitute the second most widely used category of drugs globally and account for 68 million past-year users. Amphetamines and its related analogs, including methamphetamine, have shown a remarkably spiked increase in consumption throughout the world, and considerably in the United States since 2009, and are the fastest rising drug of abuse worldwide [1]. Individuals with diagnosed methamphetamine dependence show high rates of comorbid psychiatric disorders, including primary mood, psychotic, and anxiety disorders [2]. Comparatively, hallucinogen use has shown a waxing and waning pattern, with a consumption estimate that constitutes a small fraction of stimulants [3]; this correlates with studies in animals that show that LSD and other hallucinogens are misused but are not addictive substances that lead to compulsive drug-taking, withdrawal or self-administration [4,5]. LSD has been studied for the treatment of Alcohol Use disorder [6,7], Opioid use disorder [8], Depression, and anxiety [9,10]. This case report serves to illustrate an instance where LSD showed marked symptom improvement in a patient with longstanding psychiatric conditions, including substance, mood, and trauma-related disorders.

Case Presentation

A 46-year-old Caucasian male was transferred from a Regional Hospital to a Metropolitan Academic Center Hospital after relapsing on methamphetamine and cannabis for two weeks and later attempting to commit suicide with a single dose of LSD. He was assessed to have DSM-5 diagnoses of methamphetamine use disorder, severe; methamphetamine-induced depressive disorder; and posttraumatic stress disorder, chronic.

On admission, vital signs were stable, and he was alert and oriented to person, place, time, and situation. His physical exam was grossly unremarkable. His urinary drug screen resulted positive for amphetamines and THC, and his complete blood count, comprehensive metabolic panel, urinalysis, and ethanol levels were all unremarkable.

He reported that the months before his relapse, he had felt increasing despair and hopelessness, low energy, depressed mood, anhedonia, increased sleep, and transient thoughts that he would be better off dead. Additionally, his daughter had been

murdered eight months prior, and he was in the process of a divorce from his wife, with whom he had been married for ten years. He stated that prior to this current relapse, he had been sober for about six months.

It is worth noting that he initially took LSD with the intent to end his life but stated that after the onset of its effects his outlook on life "completely changed." He reported that his mood improved and that he felt like "things were just right, and they will get better." He experienced a new sense of completeness and felt more in control of his thoughts than at any point in his history. He also saw more vivid colors and had a heightened appreciation for his sense of existence. Despite the overall improvement in his depressive symptoms and dissolution of his cravings for methamphetamine, he decided to visit a local emergency department "to make sure I'm okay... I also want to make sure that I get off meth completely".

He reported no prior psychiatric hospitalizations, outpatient psychiatry visits, or suicidal ideation or attempts. He reported increasing problems related to his methamphetamine use, including incarceration in the mid-1990s secondary to theft while intoxicated. He reported previous involvement with Narcotics Anonymous. Despite not endorsing any prior psychiatric contact, it is worth noting that he had experienced recurrent flashbacks, nightmares, and increased distress secondary to physical and emotional trauma by his stepfather when he was a child and young adult. His stepfather physically abused him for most of his childhood and adolescence, and "tried to kill" him by trying to choke him after he had sustained neck injuries in a motor vehicle accident (where he crashed his stepfather's car) and later kicked him out of the house, which led to him dropping out of school in the eleventh grade. In addition to the symptoms mentioned earlier, he dealt with anxiety related to these traumatic experiences; stating that "he never thought it was worth going to a psychiatrist for".

The patient had an uneventful two-night stay in the inpatient psychiatric unit, and no medications were initiated. Throughout his admission, he denied any psychiatric symptoms or suicidal ideation. He actively participated in groups and in therapy sessions, where he showed substantial motivation and hope for the future. At the time of discharge, the following diagnoses were given: Adjustment disorder with depressed mood; Methamphetamine induced depressive disorder, with onset during withdrawal; Stimulant use disorder, methamphetamine type, severe; Post-traumatic stress disorder, chronic; Cannabis use disorder, mild; Tobacco use disorder, mild; Hallucinogen intoxication. He was subsequently followed up on by phone call four weeks after his discharge, where he denied any psychiatric symptoms since his experience with LSD and hospitalization.

Discussion

Early studies on LSD's usefulness as a treatment for substance use were focused mainly on the treatment of alcohol and heroin dependence. These studies responded to a historical necessity secondary to the drugs of abuse with a higher incidence at that time. As substance use patterns have evolved throughout the years, a significant rise in stimulant-related disorders has become more apparent and given their high index of morbidity and mortality, and it has become more problematic. Although the neurochemical aspect of different substances differs significantly amongst themselves, the neurobiological aspect of addiction and its circuitry remains the same. Studies should focus on LSD's usefulness in the treatment of current high incidence addictive disorders, such as the stimulant use disorders, since

limited data exists for this subset of conditions.

This case report shows a specific instance where a patient suffering from long-standing comorbid mood, substance use, and trauma-related disorders achieved remission of symptoms with a single dose of LSD. It is reasonable to question if a one-time dose of any substance could be a "magical cure" for any condition. The symptomatic relief that this patient experienced was significant enough that achieved remission and remained abstinent for at least four-weeks with plans to closely follow over the coming months to further document his progression. The limitations specific to this case are related to the unknown dose of self-administered LSD and if it truly was LSD. These two variables are essential for further research in this area. This case report adds to the ever-growing list of reports that highlight the potential implications for the use of psychedelic substances in the treatment or management of patients with substance use disorders. This growing body of evidence necessitates future studies that should be rigorously designed and carried in an effort elucidate if these reports are truly a signal or just noise.

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Psychedelic-Assisted Psychotherapy Prior to Euthanasia or Physician-Assisted Suicide: Potential Implications for Future Practice

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Euthanasia or "the administration of a lethal agent by another person to a patient for the purpose of relieving the patient's intolerable and incurable suffering [1]" and its counterpart physician-assisted suicide have a long history and date back to ancient times. The Hippocratic Oath makes states explicitly "I will not give a lethal drug to anyone if I am asked, nor will I advise such a plan; and similarly, I will not give a woman a pessary to cause an abortion [2]." Hippocrates's view was not the consensus opinion as numerous Greco-Roman stories, plays, and historical documents reference and present philosophical arguments for and against the act [3]. The rise of Christianity and Judeo-Christian values more broadly influenced views on suicide and euthanasia, leading to the prohibition of the latter, and in the event of the former, all of the individual's property was confiscated by the government. In the United States, the first legal statute against assisted suicide was enacted in 1828 with several other states and localities following thereafter [4]. In the 1870s, after the advent of morphine and in conjunction with increased cancer rates, euthanasia discussions were revived under the premise of reducing pain and suffering [5].

In 1885 the American Medical Association (AMA) formally opposed euthanasia, a position it still holds. The AMA Code of Medical Ethics [1] states:

> "It is understandable, though tragic, that some patients in extreme duress—such as those suffering from a terminal, painful, debilitating illness—may come to decide that death is preferable to life. However, permitting physicians to engage in euthanasia would ultimately cause more harm than good. Euthanasia is fundamentally incompatible with the physician's role as healer, would be difficult or impossible to control, and would pose serious societal risks. Euthanasia could readily be extended to incompetent patients and other vulnerable populations. The involvement of physicians in euthanasia heightens the significance of its ethical prohibition. The physician who performs euthanasia assumes unique responsibility for the act of ending the patient's life. Instead of engaging in euthanasia, physicians must aggressively respond to the needs of patients at the end of life. Physicians:
>
> (a) Should not abandon a patient once it is determined that a cure is impossible.
>
> (b) Must respect patient autonomy.
>
> (c) Must provide good communication and emotional support.
>
> (d) Must provide appropriate comfort care and adequate pain control."

While support for euthanasia or assisted suicide ebbed and flowed throughout the first half of the 20th century, it suffered several defeats at the ballot box and was largely disowned in response to the Nazi's use of involuntary euthanasia during World War II. In the 1970s, given the advancements in medical technology, discussions surrounding the withdrawal of care and Palliative and

Hospice care again renewed conversations about euthanasia and assisted suicide. Euthanasia discussions arguably peaked in the 1990s with physician-assisted suicides by Dr. Kevorkian, including one on TV, and his eventual conviction for murder [6]. During this era, Oregon became the first state to legalize physician-assisted suicide, and the United States Supreme Court determined that there is no "right to die" in the United States Constitution [4].

After the turn of the millennium, several states passed physician-assisted suicide laws, and currently, nine states (Oregon, Washington, California, Vermont, Maine, New Jersey, Hawaii, Montana, and Colorado) and the District of Columbia allow it. In addition, other countries began to legalize physician-assisted suicide, starting with the Netherlands in 2003 and Luxembourg, Belgium, Colombia, and Canada followed over the next 15 years. Euthanasia is legal in the Australian state of Victoria, Germany, Switzerland, and the Netherlands. As a result of these measures, there has been a steady increase in the number of individuals who die from euthanasia or physician-assisted suicide [7, 8]. During this time, renewed interest in Psychedelics emerged, primarily due to the work of researchers investigating their use in patients with terminal cancer [9].

Regardless of one's personal views on euthanasia and physician-assisted suicide, it is reasonable to assume that most physicians support easing the suffering of their patients, especially in terminal conditions. Even proponents of euthanasia and physician-assisted suicide can agree that the protocols, safeguards, and laws are often not stringently followed and that this has negative ramifications for both patients and physicians [10]. Furthermore, the high rates, ranging from 25-77% [11], of concomitant depression in terminally ill patients call into question whether this may be a driving factor in a patient's decision to request euthanasia or physician-assisted suicide. Between 25-50% of patients seeking euthanasia or physician-assisted suicide showed signs of depression per a 2011 study [12], and about 1% of all euthanasia requests in the Netherlands in 2013 were for mental health reasons [12].

It is not surprising and is widely known that a patient with a cancer diagnosis is at an increased risk for suicide compared to other medical illnesses [13]. In conditions such as Amyotrophic Lateral Sclerosis, these rates are even higher [14]. The treatment of depression in terminally ill patients is also much more challenging, and evidence on the effectiveness of antidepressants is insufficient at this time [12]. While environmental and interpersonal interventions show promise at managing the symptoms of depression, an effective medication intervention would provide a much-needed benefit. It is here that Psychedelics offer a potentially novel treatment benefit.

Griffiths et al. found in their 2016 trial of psilocybin use in terminally ill cancer patients that >80% of high dose patients reported greater well-being and life satisfaction and almost 80% of patients reported improvement in symptoms of depression and anxiety at follow up six months later [9]. Literature shows that individuals who use psychedelics are at a decreased risk of suicide compared to the general population [15,16,17,18]. Additionally, numerous trials using psychedelic substances to treat psychiatric disorders in terminally ill patients have found similar results to those reported by Griffiths et. al. These include early studies such as Grof's 1973 LSD trial [19], Grob's 2010 Psilocybin trial [20], and Gasser's 2016 LSD trial [21]. In light of all of this information, should patients requesting euthanasia or physician-assisted suicide undergo a psychedelic-assisted psychotherapy session before proceeding with the euthanasia or physician-assisted suicide process?

Compared to other therapies, psychedelics are safe and generally well tolerated [22], and this appears true even in terminally ill patients, as evidenced by the aforementioned trials. Psychedelic-assisted psychotherapy offers several benefits over the standard of care therapies currently available insofar as it is typically effective with only one dose, and psychotherapy skills provided in the preparatory work are highly beneficial regardless of if a psychedelic substance follows it. Furthermore, early data indicates that psychedelics may be more effective at treating symptoms of depression and anxiety in terminally ill patients than typical psychopharmacologic agents, coupled with the anti-suicidal effects associated with psychedelic use. Psychedelics can be administered, and most settings can be adapted for sessions, meaning that these substances could be given in inpatient units, hospice houses, or even in residential context (though more strict protocols would need to be necessary).

Given the procedural and safeguard failures that have plagued the euthanasia and physician-assisted suicide communities, psychedelic-assisted psychotherapy could act as a bulwark by eliminating some of the confounding caused by depression or suicidality. These interventions are unlikely to completely eliminate the use of euthanasia or physician-assisted suicide services, but psychedelic-assisted psychotherapy offers a novel therapy option for terminally ill patients. Psychedelic-assisted psychotherapy can potentially provide patients with more meaningful days and mitigate against the symptoms of depression and anxiety, which are not well managed by current interventions These benefits should be ones that both proponents and opponents of euthanasia and physician-assisted suicide agree on and also warrant further investigation and study.

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Article

Holotropic Breathwork: A Review

John Jacob, M.D.

Abstract:
Holotropic Breathwork is a method of psychotherapy that was developed by Stanislav and Christina Grof in the mid-1970s. It is a therapeutic practice utilizing breathwork, music, and bodywork that is designed to produce an altered state of consciousness, similar to psychedelic experiences. This paper presents a review of the literature on the topic of holotropic breathwork, the components of holotropic breathwork, and the potential implications for use.
Methods: Literature Review
Results: Holotropic breathing, which uses non-ordinary states of consciousness as a therapeutic tool, deserves further con-sideration.

History and Background

Holotropic Breathwork is a method of psychotherapy that was developed by Stanislav and Christina Grof in the mid-1970s. It is a therapeutic practice utilizing breathwork, music, and bodywork that is designed to produce an altered state of consciousness, similar to psychedelic experiences induced by LSD, DMT, mescaline, psilocybin, MDMA, ayahuasca, and other entheogens [1]. This presents a non-pharmacological method to achieve non-ordinary states of consciousness in a manner that is likely less likely to have negative health effects. Suggested risks of holotropic breathwork include a possible exacerbation of underlying seizure disorder or arrhythmias, although this has not been extensively documented [2,3,4].

Main Components of Holotropic Breathwork

Breathwork

As demonstrated by history cross-culturally, many religious sects have found profound changes in consciousness can be induced by both extremes of breathing rate, hyperventilation, prolonged withholding of breath [5]. Grof described the psychosomatic response to the fear of breathing faster to be a process to counteract fear itself and one with enormous healing potential [6].

The theory behind holotropic breathwork is somewhat based on psychoanalysis. Grof feels his work reaffirms Wilhelm's Reich's observation that psychological resistances and defenses are associated with restricted breathing [7]. He notes that an increase in the pace of breathing typically loosens psychological defenses and leads to a release in the emergence of an unconscious or superconscious material [8].

Music

Like breathing, many pre-industrial cultures independently developed drumming rhythms, chants, and music in general that have since been shown to have a demonstrable effect on brain activity [9,10,11]. He notes that cultural anthropologists have cited numerous cross-cultural examples of trance-inducing methods of an extraordinary power by use of sound [12,13]. Grof carefully selected music to serve several important functions. He felt that it would immobilize emotions associated with repressed memories, bring them to the surface, and facilitate their expression [14]. He felt that it helped open the door into the unconscious, intensified and deepen the healing process, and provided a meaningful context for the experience. He describes the continuous music as creating a "carrier

wave" that helps individuals move through difficult experiences, overcome psychotic defenses, and to surrender [6].

He notes that music has an additional important function in the group setting. It masks the noises made by participants and merges them into a complex aesthetic form. He advises completely surrendering to the flow of the music during a holotropic therapy session, even if this leads to crying, shaking, laughing, or screaming. The recommended musical pieces are those which are unfamiliar, perhaps not in the native tongue of the listener. Grof describes five musical phases of the session: opening music, trance-inducing music, breakthrough music, heart music, and meditative music [7,8].

As a summary, the music begins as dynamic and emotionally uplifting. It gradually increases in intensity, and culminates into "breakthrough music" such as orchestral pieces or dramatic movie soundtracks, about an hour and a half into the session. The intensity of the music then decreases, terminating in a more soothing and meditative manner [7,8].

Bodywork

Grof also describes the importance of the physical response induced by holotropic breathwork. The physical response to hold the breathwork varies considerably from one person to another. Most commonly, faster breathing brings, at first, intense psychosomatic manifestations [5]. These are, at times, in line with what is known as hyperventilation syndrome. This is a stereotypical pattern and physiological response that consists primarily of tensions in the hands and feet [15,16].

Grof notes that through his many holotropic breathing sessions, that fast breathing carried over a 3 to 4 hours does not seem to lead to the classical hyperventilation syndrome, but rather a progressive relaxation, sexual feelings, and even at times mystical experiences. He states that during a session, when individuals develop carpopedal spasms, they tend to be self-limited [6]. Grof argues that, at times physical manifestations that develop during the breathing in various areas of the body are not merely physiological reactions to hyper-ventilation but may have complex psycho-somatic structure and usually have a specific psychological meaning for the individuals involved [17]. The intense rhythmic breathing is said to produce increasing tensions in the body that reaches a climax and is followed by a profound relaxation [6].

Grof describes two mechanisms behind this phenomenon. The first mechanism he relates to the "catharsis and abreaction" similar to Sigmund Freud and Joseph Breuer's study of hysteria. According to Grof, pent-up physical energies are discharged through tremors, twitches, dramatic body movements, coughing, and vomiting. The second mechanism Grof describes takes the form of "unrelenting muscular contractions of various duration, which he describes as "tetany." In this, the participant uses lots of pent-up energy through repeated tensions, causing a deep relaxation to follow [6].

Nourishing Physical Contact

Grof also encourages the use of "nourishing physical contact" during therapy sessions. This can be in the form of hand-holding or touching the forehead. Grof emphasizes the importance of obtaining the participant's consent for this and recognizing boundaries. This physical contact can be used to heal traumas caused by neglect, abandonment, or other emotional trauma, similar to the method termed "fusion therapy" [6]. This therapy was developed by London psychoanalysts Pauline McCrirck and Joyce Martin, in which

they use close physical contact with LSD to heal their patient's traumas [18].

Mandala Drawing

After the breathing sessions, participants express their experiences by drawing mandalas. The term "mandala" comes from the classical Sanskrit language and generally translates to circle [19]. A mandala is generally a term for a design with geometrical symmetry, for example, a spiderweb or flower. Many ancient cultures have widely used mandalas. In the Western world, they were first used as therapy by Carl Jung, who described the mandala as a "psychological expression of the totality of the self" [20].

There is some evidence that Mandala therapy may benefit those suffering from PTSD. There is limited research on using mandalas in therapy, but current literature is investigating the use of art in the treatment of anxiety and the ability to increase mindfulness [21,22].

Following a holotropic breathwork session, the participants are asked to meditate on their experience and try to depict the session by drawing a mandala. Grof does not give specific guidelines for the mandala drawing. He encourages various forms and notes that the mandala drawing may either be representative of the immediately preceding session or may also anticipate events of the next session. Grof explains this phenomenon with Jung's idea that "the psyche cannot be fully explained from preceding events [6]."

Group Sharing

After the Mandala drawing, participants bring their mandalas to a group sharing session. Facilitators encourage participants to openly discuss their experiences. In contrast to the usual psychotherapeutic practice, facilitators are discouraged from interpreting the experiences of the participants. Instead, Grof encourages facilitators to ask questions to help the participant discover their own interpretation. Grof also notes that if the experiences contain archetypal content, it may be useful for facilitators to point out parallels shared by mythological motifs from other cultures, a method termed "amplification" from C.G. Jung [6,23].

Physiologic Mechanism of Action

The mechanism behind holotropic breathing is not entirely known. Grof proposes that it is similar to the physiology of breathing at high altitude. In high altitude, an increased respiratory rate and depth compensate for a lower oxygen partial pressure in the air and decrease carbon dioxide blood levels. This decrease in brain CO2 partial pressure and concomitant increase in pH is known as respiratory alkalosis, which has neurophysiologic effects. It is thought that the cerebral cortex is the most sensitive to this change, and it is thus temporarily inhibited [24]. In this state, trans-personal experiences may be revealed. As Grof points out, this may be why individuals from cultures who live in high altitudes are known for their spirituality [6,9].

In a relaxed state, inspiration consists of the diaphragm moving downwards and the abdominal wall and muscles moving outward as the upper rib cage expands [25]. Normal relaxed breathing is effortless and rhythmic. Studies show that inhibited breathing is a response to uncomfortable experiences. For example, people in a public work environment showed sustained inhibited breathing patterns compared to being at home. Inhibited breathing is characterized by an extended, over-controlled exhalation, delayed onset of inspiration, and shortened duration of inspiration. Breath-holding can occur in extreme cases [4].

This inhibited breathing pattern has several implications. First, the suppression of

breathing is associated with increased CO2 levels and blood pressure, which is associated with increased anxiety and poor mood [26]. This points towards a positive feedback loop, in which anxiety leads to breathing suppression, which furthers anxiety.

Inhibited breathing also affects neurologic functioning. During breathing suppression, less oxygen is exchanged in the blood. The brain has little to no reserve of oxygen in the blood and is therefore sensitive to oxygen deprivation. This depletion in oxygen may affect energy production and serotonin synthesis [27].

Suggested Efficacy

To date, there have been very few studies on the effects and uses of holotropic breathwork.

A 1996 study investigated the relationship between the use of Holotropic Breathwork and therapeutic changes in levels of distress associated with self-identified problems, death anxiety, self-esteem, and a sense of affiliation with others. Those who received both breathwork and therapy showed significant reductions in death anxiety and an increase in self-esteem compared to those only receiving therapy [28].

Dr. James Eyerman conducted a 2013 report on approximately 11,000 psychiatric inpatients who participated in holotropic breathwork over a 12-year period (from 1989 to 2001). 82% reported transpersonal experiences. Dr. Eyerman also includes two case reports of patients during the breathwork, who achieved metaphysical experiences that helped them overcome their trauma and depression [29].

A 2015 study examined temperament changes of 20 people after four sessions of holotropic breathwork. The study used the Temperament and Character Inventory (TCI-R), validated by Cloninger. The participants showed positive changes in temperament and character following holotropic breathwork. All 20 participants also experienced a significant reduction in interpersonal problems and described an increase in self-awareness [14].

While the research on holotropic breathwork specifically is sparse, there is a large body of research on the effects of meditation on anxiety, depression, and overall mental well-being. Meditation, which involves focusing on deep, slow breathes as part of the practice, shares many components of holotropic breathwork. A 2014 meta-analysis included 47 trials that met criteria for well-designed studies. The findings suggest that mindful meditation can help ease anxiety, depression, and pain [30]. Currently, there is ongoing research on the role psychedelics may play in mental health. Holotropic breathing, which uses non-ordinary states of consciousness as a therapeutic tool, also deserves further consideration.

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Case Report: Hallucinogen Persisting Perceptual Disorder

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Abstract:
A 20-year-old male reported symptoms of persisting perceptual disturbances the failed to remit completely. The patient met DSM-V criteria for Hallucinogen Persisting Perceptual Disorder and reported visualizations, perception of movement in still images, and fractal patterns. The patient responded to treatment with Risperdal initially, followed by Zoloft over the course of two years.

Introduction

Since the advent of hallucinogen use by human beings, there have been reports of persisting effects, though not much has been systemically and rigorously studied. Hallucinogen persisting perceptual disorder (HPPD) is a rare disorder that has no definitive treatment or known prevalence. According to DSM-V, prevalence is estimated to be low, approximately 4.2% [2], but this has not been fully evaluated [1]. HPPD is characterized by a persisting, chronic alteration in perception that causes distress or impairment in functioning. The duration of onset of persisting perceptual disturbances post hallucinogen use is poorly defined. There is no set period of sobriety required; however, the hallmark feature is that these perceptual disturbances persist in the absence of continued drug use and cause distress or impairment.

HPPD was first described in 1954, in a study that reported using Lysergic acid diethylamide (LSD) in 36 "psychoneurotic patients" over one year [3]. A definition of persisting perceptual disturbances was described with the term "flashbacks" in 1969 by Horowitz, who classified three separate types of perceptual disturbances: perceptual distortions, heightened imagery, recurrent unbidden images [4]. Thirty-one subjects were interviewed in the Haight-Ashbury community of San Francisco in 1969, and 8 reported flashbacks, but all eight subjects continued to use drugs at the time and were intoxicated with various substances, marijuana and secobarbital at the time of flashback [4].

However, not until 1986 was HPPD classified as a distinct clinical entity with diagnostic criteria in the DSM-III-R [5]. According to the DSM-V, perceptual symptoms may consist of geometric hallucinations, false perceptions of movement in peripheral visual fields, flashes of color, intensified colors, trails of images of moving objects positive afterimages, halos around objects, macropsia, micropsia. The DSM-V defines HPPD according to the following criteria:

A. Following cessation of use of hallucinogen, the re-experiencing of one or more of the perceptual symptoms that were experienced while intoxicated with the hallucinogen

B. The symptoms in Criterion A cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The symptoms are not attributable to another medical condition and are not better explained by another mental disorder or hypnopompic hallucinations [2]

The term "flashback" itself is problematic as there are poor descriptions of this term in the context of HPPD. Flashbacks may represent "instances of normal memory accompanied by emotional distress so upsetting to a subset of individuals that their clinicians are informed of them [6]." Flashbacks occur in the setting of PTSD, and there

is difficulty with assessing flashbacks in varying clinical contexts. Outside of the DSM-V, there have been two "types" of HPPD described [7]. Type I or HPPD I, is a short-term non-distressing, benign, reversible state that may be accompanied by pleasant affect [7]. Type 2 or HPPD II is described as a severe, persistent state, that may occur with an aura, irreversibility, sharp depersonalization or derealization. Either Type I or Type II HPPD may occur intermittently and or suddenly. The duration of episodes may be shorter for HPPD I than HPPD II [7].

The content of visual and perceptual disturbances varies widely, which is another difficulty in clinically evaluating this syndrome. Visualizations of dots or specks when entering a darkened room, fractals, repetition or moving patterns, sharp color contrasts, superimposition of geometric patterns, monochromatic vision, recurrent synesthesia, geometric phosphenes, imagistic phosphenes, acquired dyslexia, and aeropsia [8]. Specific triggers have been reported and are listed as entering a darkened room, sexual intercourse, pregnancy, delivery, postpartum, flashing lights, tobacco smoking, use of phenothiazines, Risperdal, and ECT in patients with a history of LSD use [8,9]. LSD use has been associated with HPPD, as compared to psilocybin [10]. A study performed on 500 Native American church members, who ritually ingested peyote, evaluated for residual neuropsychological effects, including perceptual disturbances as in HPPD. In this Navajo community, each member had ingested peyote on at least 50 occasions over three years and demonstrated zero cases of HPPD [1].

Case Report

An unemployed, 20-year-old, male patient reported recreational use of multiple substances starting at age 13. The patient reported the first use of alcohol and marijuana at age 13, with use occurring approximately twice weekly. At age 14-15, the patient began to experiment with psychedelics, starting with marijuana. Marijuana use increased to daily use by age 15-16. By age 18, the patient had used LSD, psilocybin, DMT, and dextromethorphan (via cough syrup). Total LSD use was approx.-imately 50-60 times over the ages of 14-18, and the patient continued to use LSD 3-4 times per year after 18. Additionally, the patient reported using psilocybin 30-40 times and dextromethorphan more than ten times in total. The patient denied the use of mescaline, ayahuasca, or ketamine. The patient endorsed an unknown frequency or duration of abuse of other drugs. The patient reported abuse of amphetamines (Adderall and Ritalin), cocaine, nitrous oxide, and MDMA (ecstasy) with undefined frequency, duration, or age at first use. The patient denied a history of heroin use or any intravenous drug use. The patient reported abuse of benzodiazepines including Klonopin, Ativan, and Xanax. The patient was unable to state the frequency or duration of use but reported the first use of Xanax at age 17. The patient reported taking benzodiazepines whenever they were available to him but denied daily use.

The patient was admitted for psychiatric hospitalization due to an unintentional overdose of thienodiazepine. The patient had ordered etizolam over the internet, a thienodiazepine, which is a benzodiazepine analog, that is unavailable in the united states. The patient denied a depressed mood, anhedonia, sleep disturbance, low energy, appetite changes, or decreased concentration. The patient adamantly denied a suicide attempt. The patient reported that prior to the hospitalization he had used an unknown amount of etizolam, alcohol, and marijuana. The patient was disorganized at the time of admission, likely due to acute

intoxication, and reported paranoid delusions of people being after him.

Once the patient was medically stable and no longer intoxicated, he reported several perceptual disturbances that had persisted since approximately age 18. The patient reported visualization of specks, sometimes colored, when entering a darkened room. He reported colored fractal patterns when closing his eyes for a prolonged period, mostly noted when attempting to fall asleep. The patient reported slightly swirling repetitive motions when viewing certain works of art, grass, furniture textures, or clouds. During hospitalization, the patient had a psychedelic-themed t-shirt and frequently mentioned he could see the image move in a wave-like pattern. This movement was not constant but would persist for 20-30 minutes or until the patient reported no longer attending to the image. The patient reported noticing these disturbances around age 18 during a time when he was on vacation with his family and had ingested no illicit substances for a week before the disturbance. The patient reported that he would notice worsening of the perceptual disturbances when he was acutely intoxicated. The patient denied that these visual disturbances were distressing.

The patient also had significant persecutory delusions concerning his parents being involved in a conspiracy against him with an unknown number of other people. He felt that the people involved would monitor him through unknown means and steal various items from him. The delusions did not extend to thought broadcasting, thought insertion, or delusions of reference. The patient denied auditory hallucinations or olfactory hallucinations. The patient could not describe the specific events in great detail and would perseverate on his personal items being stolen. He denied this conspiracy was global, but that it extended past his immediate family members. The patient was unable to describe the conspiracy in a linear fashion and would become frustrated, attempting to articulate how he knew of such a conspiracy.

Collateral taken from the patient's mother and father suggested significant social and occupational impairment secondary to persistent hallucinations. The patient was unable to perform daily tasks such as laundry, routine bathing, a consistent sleep-wake schedule, employment, or attending school. The patient graduated high school. The family did not report any significant cognitive decline outside of acute drug use. The family reported that the patient had not expressed delusions prior to hospitalization, but that he had expressed similar persecutory delusions under the acute influence of substances. The family was unsure of which specific substances the patient had been using when endorsing delusions, other than marijuana and alcohol. The family was unsure of funding for the patient's drug use and reported suspecting that the patient was dealing drugs.

The patient himself denied any impairment or distress from persistent perceptual disturbances. The patient had difficulty maintaining focus and attention on a conversation and would frequently stare away from the conversation to attend to a perceptual disturbance. The patient would then deter the conversation away from the topic and insist on commenting on the perceptual disturbance with detailed descriptions. The patient also repeatedly reported depersonalization at times that started around age 19. The patient reported improvement in his depersonalization symptoms during the hospitalization. The patient had only reported a sense of derealization during or within 24 hours of acute drug use, most notably psychedelics, LSD, or psilocybin. The patient did also report derealization when acutely intoxicated on

etizolam, alcohol, and marijuana that improved with sobriety.

The patient was hospitalized for a total of five days, with diagnosis of substance-induced psychosis (etizolam, alcohol, and cannabis) and HPPD (delusions and perceptual disturbances). The patient also met criteria for cannabis use disorder, severe. The patient was started on Risperdal 0.5mg and then increased to 1mg at bedtime. Though perceptions continued to occur, he denied symptoms for two days prior to discharge. The patient reported improvement in delusions and no longer felt his parents were in on the conspiracy, but he continued to express doubts about others being responsible for stealing his things. The patient had improved insight and judgment and demonstrated a linear thought process by the time of discharge.

The patient was followed for two years in the psychiatric outpatient clinic and reported resolution of depersonalization and delusions within the first year. He remained on Risperdal for six more months and was subsequently titrated off without issue. The patient was started on Zoloft 100mg for anxiety due to reduced drug use. The patient reported daily marijuana use, with infrequent 3-4 day periods of abstinence due to the cost. He continued to report occasional spontaneous perceptual disturbances with decreased frequency. All perceptual disturbances remained non-distressing to patient. The patient did not have any continued delusions or recurrence of psychotic symptoms at the time of follow up.

Discussion

Given the patient's age and extensive drug abuse history, schizophrenia could not be completely ruled out during the hospitalization. The patient did not meet the full criteria for schizophrenia during the hospitalization or at follow up for two years. In the literature, risperidone has conflicting evidence to improve HPPD, some studies report worsening symptoms with atypical antipsychotics. Benzodiazepines may be more beneficial than atypical antipsychotics [11]. In a case report of two patients diagnosed with "post-LSD schizophrenia," the administration of risperidone 3 mg daily resulted in the resolution of transient visual disturbances with continued antipsychotic therapy [12]. Another case report reported the initial worsening of HPPD symptoms with olanzapine and an SSRI, followed by improvement of symptoms with continued treatment [13]. The patient appeared to meet a transient, non-distressing definition of HPPD I, though these criteria are not currently included in the DSM-V [2]. The patient continued use of marijuana may have contributed to some persisting effects of the perceptual disturbances, but the lack of spontaneous recurrence during periods of sobriety is more consistent with HPPD. It is reasonable to theorize that the patient may have further improvement in HPPD frequency, severity, and duration if complete abstinence from marijuana were to occur.

The neurological basis for a persisting perceptual disorder after acute or chronic use of hallucinogens is still unclear. The volume of grey matter in the temporal and frontal lobes increases during early childhood and then decreases over the course of adolescence [14]. These changes are consistent with the pruning of neuronal processes and synapses in adolescence. At-risk individuals who go on to develop psychosis exhibit an accelerated rate of grey-matter loss in the frontal lobe compared with those who do not [15]. Heavy drug use affecting developing areas of the brain that determine visual processing may theoretically contribute to persisting alterations in perception. The pharmacological basis for this remains unclear, but some alternatives for clinical treatment should be considered. Lamotrigine may demonstrate a

neuroprotective effect and help to reduce symptoms of HPPD, particularly depersonalization and derealization [16]. Naltrexone and clonidine have been used successfully, and so have benzodiazepines, propranolol, risperidone, and SSRIs [17]. HPPD symptoms may be confounded due to continued drug use, underlying psychotic or mood disorders, or inability to obtain a detailed history. Due to the low prevalence, lack of diagnostic clarity, and several confounding factors, HPPD is challenging to diagnose and treat. Success in clinical treatment, like with much of psychiatry, depends on individualizing treatment to the specific patient and taking into account the biopsychosocial aspects of care.

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