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BRIEF COMMUNICATION

3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for victims of sexual abuse with severe post-traumatic stress disorder: an open label pilot study in Brazil

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Objective: To conduct Brazil's first clinical trial employing 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder (PTSD), given its high prevalence resulting from epidemic violence.
Methods: Of 60 volunteers, four matched the inclusion & exclusion criteria. Three patients with PTSD secondary to sexual abuse (diagnosed by the Structured Clinical Interview for DSM-IV and the Clinician Administered PTSD Scale for DSMV-4 [CAPS 4]) completed enrollment and treatment, following a standardized Multidisciplinary Association for Psychedelic Studies protocol consisting of 15 weekly therapy sessions: three with orally administered MDMA with concurrent psychotherapy and music, spaced approximately 1 month apart. CAPS-4 scores two months after the final MDMA session were the primary outcome.
Results: No serious adverse events occurred. The most frequent adverse events were somatic pains and anguish. CAPS-4 reductions were always greater than 25 points. The final scores were 61, 27, and 8, down from baseline scores of 90, 78, and 72, respectively. All reductions were greater than 30%, which is indicative of clinically significant improvement. Secondary outcomes included lower Beck Depressive Inventory scores and higher Post-Traumatic Growth Inventory and Global Assessment of Functioning scores.
Conclusions: Considering the current limitations in safe and efficacious treatments for PTSD and recent studies abroad with larger patient samples, MDMA-assisted psychotherapy could become a viable treatment in Brazil.
Clinical trial registration: RBR-6sq4c9

Keywords: MDMA; PTSD; psychotherapy; sexual abuse; psychedelics

Introduction

Brazil suffers from increasing rates of violence and associated mental health problems. According to a survey of 3,744 individuals, more than 80% of the population in the metropolitan Rio de Janeiro and São Paulo have experienced traumatic events in their lifetime, with rape or sexual molestation ranging from 1.3 to 4.9%. Five percent of the general population met post-traumatic stress disorder (PTSD) diagnostic criteria in the previous year, and 10% have met PTSD diagnostic criteria in their lifetime.[1]

Although various psychological and pharmacotherapeutic treatments exist for PTSD, including current first-line treatments involving combinations of pharmacology and psychotherapy,[2] treatment response is insufficient for a considerable proportion of patients.[3] One promising alternative under development abroad is 3,4-methylenedioxymethamphetamine-assisted psychotherapy (MDMA-AP), which was granted a "breakthrough therapy" designation by the U.S. Food and Drug Administration after completing Phase 2 trials.[4-6] MDMA-AP is currently under assessment in a multi-site Phase 3 trial,[7,8] and thus is a strong candidate for approval as a treatment for PTSD.

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Consequently, we were interested in determining whether the methods and premises of MDMA-AP would be efficacious in a Brazilian sample of PTSD patients. Given the high national prevalences of sexual abuse and molestation,[1] the high conditional risk of developing PTSD,[9] and specific challenges in the treatment of this deleterious form of trauma,[10] we conducted the first clinical trial of MDMA-AP in Brazil, following the same methodology developed abroad.[11]

Methods

Sample and procedures

Participants were recruited through social media, the Brazilian press, medical referrals, and word of mouth. The treatment design strictly followed an open source treatment manual[11] and previous Phase 2 studies.[4-6] The design included three preparatory psychotherapy sessions followed by three monthly cycles, each consisting of one MDMA-AP session followed by three integrative psychotherapy sessions. Each preparatory and integrative session lasted 90 minutes, and each of the three MDMA-AP sessions lasted 8 hours. The dosage was 75 mg in the first session, and 75 or 125 mg in the second and third sessions, according to a joint decision by the participant, the physician, and the therapist. A supplemental dose of 50% the initial dose was offered 90 to 120 minutes after initial dose. The psychotherapists (AJ and DJ), the physician responsible for drug administration and monitoring (BRC), and the principal investigator (EES) completed the MAPS training program for MDMA-AP in the USA before the study began.

The inclusion criteria were: a DSM-IV PTSD diagnosis according to the Structured Clinical Interview for DSM-IV and the Clinician Administered PTSD Scale for DSMV-4 (CAPS-4) for at least 6 months; a CAPS-4 score > 60[4-6]; a minimum of 18 years of age; at least one previous treatment failure (either psychotherapy or pharmacotherapy); willingness to abstain from psychiatric medications (as determined by the research team), herbal supplements, any non-prescribed medications, and any illicit drugs; alcohol abstinence for 24 hours prior to the MDMA-AP sessions; nicotine and caffeine abstinence for at least six hours after MDMA administration; refraining from driving or operating machinery for 24 hours after MDMA administration; negative pregnancy tests and a willingness to comply with continuous contraceptive use; providing an emergency contact; fluency in Portuguese; having completed middle school (the 8th grade); granting permission to record all sessions (audio and video); agreeing not to enroll in any other concurrent study.

The exclusion criteria were: pregnancy or potentially fertile women who do not use contraceptives; a history of primary psychotic disorder, type 1 bipolar disorder or personality disorder; evidence or a history of coronary artery disease or peripheral vascular disease; hepatic disease (except asymptomatic Hepatitis C) or any other condition that could increase the risks of administering MDMA; hypertension; weight below 48 kg; a history of hyponatremia or hyperthermia; presenting a serious suicide risk according to the Columbia Suicide Severity Rating Scale; presenting a serious risk of injuring others; having used illegal drugs (including ecstasy) more than 10 times in the last ten years or at least once in the past six months; requiring psychiatric medications during the study; a DSM-IV diagnosis of drug abuse or dependence (except for nicotine and/or caffeine); inability to provide informed consent; any other medical or psychiatric condition that could potentially interfere with study participation.

Outcomes

The primary outcome was the CAPS-4 score at baseline and two months after the final MDMA-AP session. The pre- and post-treatment CAPS-4 scores were used to estimate the effect size using Rosenthal's r[12] in Stata® statistical package (v.12). Secondary outcomes included PTSD symptoms according to the PTSD Checklist – Civilian Version,[13] total scores on the Post-Traumatic Growth Inventory,[14] suicidal ideation and behavior according to the Columbia-Suicide Severity Rating Scale,[15] depressive symptoms according to the Beck Depression Inventory-II, Dissociative Experience Scale-II results,[16] sleep quality according to the Pittsburgh Sleep Quality Index,[17] and the DSM-IV Global Assessment of Functioning. The subjective effects of MDMA were assessed with the Mystical Experience Questionnaire[18] and the Subjective Units of Distress Scale.[4-6] Change in secondary outcomes was calculated as the difference between scores at baseline and two months after the final MDMA-AP session, which was interpreted using the standard cut-off points or score ranges of each instrument.

Ethics statement and controlled substances

The protocol was developed in accordance with the Declaration of Helsinki, national regulations and international standards for medical research. It was approved by the National Research Ethics Commission (CONEP; CAAE 46252015.2.0000.5511), registered in the Brazilian Clinical Trials Registry (ReBEC; RBR-6sq4c9), and was publicly announced prior to recruitment. Authorization to possess and use MDMA for this study was issued by the Brazilian Health Surveillance Agency (ANVISA: Portaria 344/1998), which regulates scientific research with controlled substances. An export permit was issued by the U.S. Drug Enforcement Administration, and an import permit was issued by ANVISA. The MDMA was manufactured by Dr. David Nichols at Purdue University and supplied for this study by the Multidisciplinary Association for Psychedelic Studies (MAPS).

Results

Although 60 volunteers expressed interest in participation, only 24 underwent the screening process. The remaining volunteers were not screened due to distance to from the study site, scheduling conflicts, exclusionary medical histories, or non-responsiveness. Of the 24 volunteers who completed psychiatric screening, only nine met the criteria for PTSD diagnosis. Five had comorbidities or

met other exclusion criteria. Four met all inclusion criteria, but one did not complete enrollment due to an untreated infection. Thus, three participants (one male and two female) were enrolled in the study. All three were victims of sexual abuse: one as an adult and two during childhood. One was Afro-Brazilian and two were Caucasian. They were 45, 35 and 41 years of age. One was married, one was divorced, and one was single.

Since all participants opted for supplemental doses in all MDMA-AP sessions, the total dosage reached 112.5 mg in the first and 187.5 mg in the second and third MDMA-AP sessions. There were clear changes in emotion, cognition, blood pressure, heart rate and temperature (Table S1, available as online-only supplementary material).

There were no serious adverse events, either related or unrelated to MDMA. In all, 54 adverse events occurred during the nine preparatory sessions, 20 during the nine total MDMA sessions, and 73 during the 27 total integrative sessions (Table 1). Somatic pain was the most frequently mentioned event during the preparatory and MDMA-AP sessions (seven and four occurrences, respectively), while anguish was the most frequently reported event during the integrative sessions (16 occurrences).

Considerable reductions in the primary outcome (CAPS-4 score) occurred for all patients. The baselines scores, 90, 78, and 72, dropped to 61, 27 and 8 at the primary endpoint, i.e. reductions of 29, 51 and 64 points, respectively ($z = 1.604$, $r = 0.924$ and $p = 0.108$). Secondary outcomes included improvement in PTSD symptoms according to PTSD Checklist – Civilian Version scores, post-traumatic growth according to Post-Traumatic Growth Inventory scores, reduced depressive symptoms according to Beck Depression Inventory-II scores, and improved general functioning according to Global Assessment of Functioning scores. Changes in sleep quality and dissociative symptoms were mild (Table 2).

Discussion

The three participants were all victims of sexual abuse, one of the most deleterious forms of trauma, which severely impacts mental health and psychopathology,[10]

Table 1 Frequency of spontaneously reported adverse events by session type in three PTSD patients

Session type	Preparatory	MDMA	Within 7 days after MDMA sessions	Other integrative sessions	Total
Total number of sessions	9	9	9*	18	45†
Abdominal pain	4	1	1	0	6
Anguish	3	2	10	6	21
Anxiety	5	0	0	2	7
Chest pain	1	0	0	0	1
Colic	3	2	0	2	7
Cough	3	3	2	3	11
Crying	0	0	0	2	2
Depression	1	0	0	1	2
Despair	0	1	0	1	2
Diarrhea	1	0	0	0	1
Dizziness	1	1	0	0	2
Drowsiness	2	0	0	0	2
Fear	3	0	1	3	7
Frustration	1	0	0	0	1
Headache	2	0	3	1	6
Impotence	2	0	0	0	2
Insomnia	0	1	0	0	1
Irritability	0	1	0	1	2
Jaw tension	1	0	0	0	1
Lack of libido	0	0	0	1	1
Lack of trust	0	0	0	1	1
Loneliness	0	0	0	2	2
Muscle tension	0	0	1	1	2
Nasal congestion	0	1	0	0	1
Nausea	1	0	0	1	2
Nightmares	1	0	1	1	3
Panic	2	0	0	1	3
Rage	0	1	0	2	3
Ruminative thoughts	1	0	0	0	1
Sadness	3	1	0	2	6
Fear	0	0	0	1	1
Shortness of breath	1	0	0	0	1
Sleeplessness	0	0	1	0	1
Somatic pains	7	4	3	8	22
Stress	1	0	0	0	1
Fatigue	3	1	3	2	9
Vulnerability	1	0	0	2	3
Total	54	20	26	47	147

MDMA = 3,4-methylenedioxymethamphetamine; PTSD = Post-traumatic stress disorder.
* Plus 63 phone contacts, daily during the first week post MDMA sessions.
† Not counting phone contacts.

Table 2 Primary and secondary outcome measures before (baseline results) and after treatment (final results) in three PTSD patients

Instrument/session	Patient 1	Patient 2	Patient 3
CAPS-4			
Baseline	90	78	72
Final	61	27	8
PCL-C			
Baseline	69	59	55
Final	57	49	20
PTGI (total)			
Baseline	9	34	11
Final	66	86	60
C-SSRS SI/II/SB			
Baseline	35,308	35,338	35,369
Final	1/9/NA	1/11/NA	0/0/0
BDI II			
Baseline	43	30	43
Final	16	10	2
DES II			
Baseline	23	32	44
Final	28	32	6
PSQI (total)			
Baseline	11	11	11
Final	9	7	5
GAF			
Baseline	45	45	45
Final	55	75	85

BDI II = Beck Depression Inventory II; CAPS-4 = Clinician-Administered PTSD Scale for DSM-IV; C-SSRS = Columbia-Suicide Severity Rating Scale; DES II = Dissociative Experience Scale; GAF = Global Assessment of Functioning; NA = not available; PCL-C = PTSD Checklist-Civilian Version; PSQI = Pittsburgh Sleep Quality Index; PTGI = Post Traumatic Growth Inventory; PTSD = Post-traumatic stress disorder.

and met the criteria for severe PTSD (according to baseline CAPS-4 scores). All three patients benefited from MDMA-AP treatment: one showed small but clinically significant improvement in the primary outcome (a 29-point [32%] reduction in CAPS-4 score), one showed moderate improvement (a 51-point [65%] reduction), and one showed strong improvement (a 64-point [89%] reduction). The effect size (r = 0.92) was large, but this must be interpreted with care due to small sample size. Nevertheless, two recent meta-analyses with larger samples confirmed that MDMA-AP for PTSD has large effect sizes.[19,20] The improved CAPS-4 scores observed in the present study were further supported by reduced PTSD symptoms according to the PTSD Checklist – Civilian Version: one patient's scores dropped from the high severity to the little or no severity range, while the other patients' scores dropped approximately 20 points, although they remained in the high severity range. Improvements were also seen in post-traumatic growth according to Post-Traumatic Growth Inventory scores: dramatic increases occurred in two cases (5-fold and 7-fold, for patients 1 and 3, respectively), while a considerable (2.5 fold) increase occurred in patient 2. Furthermore, considerable reductions occurred in depressive symptomatology according to Beck Depression Inventory-II scores: patient 1 dropped from severe to mild, and patients 2 and 3 dropped from severe to minimal, with final BDI scores of 10 and 2, respectively. Changes in dissociation symptoms and sleep quality were minimal according to the Dissociative Experience Scale-II and Pittsburgh Sleep Quality Index results, while Global Assessment of Functioning scores improved from serious to moderate in patient 1, from serious to mild in patient 2, and from serious to slight in patient 3 (Table 2).

Importantly, there were no serious adverse events, no cases of hyperthermia, and an acceptable level of adverse events (which were tolerable and short-lived). Nevertheless, it is important to consider this study's limitations, including the small sample size and the open-label design, which could hinder conclusions about caregiver effect.

These results compare fairly with previous Phase 2 MDMA-AP studies, which have reported an overall success rate of about 60% in more than 100 severe PTSD cases.[4-6,21] Although our sample size limits any definitive conclusions, it is enough to warrant further MDMA-AP studies in Brazil. These efforts are especially warranted here due to the epidemic levels of violence and high prevalence of PTSD,[1] a condition for which current treatments are ineffective for a considerable proportion of patients. Furthermore, additional studies are justified considering that a Phase 3 MDMA-AP for PTSD trial is now underway, with potential approval anticipated in a few years.[7] To our knowledge, this is also the first scientific study in Brazil to administer a controlled psychedelic substance to a clinical population. Considering the recent surge of research on the therapeutic potential of psychedelics, especially when combined with psychotherapy,[22] our results should encourage further Brazilian research about the therapeutic potential of this class of drugs.

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Disclosure

The authors report no conflicts of interest.

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