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Clinical Evidence for the Use of Methylone in the Treatment of PTSD: A Case Series with Long-Term Follow-Up

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Abstract

Background: The Rapid Acting Empathogen (RAE) 3,4-methylenedioxy-N-methylcathinone (methylone; also known as MDMC, βk-MDMA, and M1), is a phenethylamine compound with chemical and pharmacological similarities to 3,4-Methylenedioxymethamphetamine (MDMA). It has been used outside of medical settings to treat Posttraumatic Stress Disorder (PTSD) and depression with encouraging preliminary clinical outcomes. A recent observational study comparing the acute effects of methylone and MDMA in healthy participants reported that while the subjective drug effects of the two drugs were categorically similar, methylone demonstrated significant clinical, physiological, and pharmacological differences, including "softer" empathogenic and psychostimulant effects that may have potential for accelerated adoption across a broader range of medical settings and clinical applications.

Objective: Here we present clinical experience with 21 patients (57% female) treated with one or more oral doses of methylone for PTSD in a naturalistic setting.

Methods: Archival data was used to examine patient characteristics.

Results: Methylone was well tolerated. All patients achieved at least "minimal improvement" following treatment and 81% were "much" or "very much" improved on the Clinician Global Impressions Scale.

Conclusion: There is an urgent need for rapid-acting and robust interventions for PTSD. These promising acute therapeutic outcomes warrant controlled trials to further characterize the role of methylone as a monotherapy and augmentation in the pharmacotherapy of PTSD.

Keywords: Posttraumatic stress disorder; PTSD; Methylone; Treatment; Case series; Rapid Acting Empathogen (RAE)

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Introduction

PTSD is a debilitating, and often chronic, psychiatric disorder characterized by a constellation of symptoms including intrusive re-experiencing, avoidance of trauma-related stimuli, negative cognition and mood, physiological reactivity and increased arousal, and clinically significant distress and impairment in functioning [1]. Available pharmacotherapy options are limited. Selective Serotonin Reuptake Inhibitors (SSRIs) represent the first-line pharmacological treatment; paroxetine and sertraline are the only FDA-approved medications for PTSD. Despite their established efficacy, these treatments are sub-optimal. They are slow-acting antidepressants with a

delayed onset of action - at least 4 weeks of continuous treatment for clinical benefit [2-4]. This latency period is troubling, as it increases risk for suicide and self-harm as well as other potentially destructive behaviors [5,6]. Even when optimally delivered, 40% of patients do not respond to SSRIs, only 20% to 30% achieve remission, and the magnitude of the difference from placebo ranges from 10% to 20% [7]. Rates of non- or partial response to SSRIs among individuals with chronic and complex PTSD such as military veterans, are comparable to or worse than those of the civilian patient population [8,9]. Furthermore, many who are classified as 'treatment-responders' remain symptomatic and continue to lead restricted lives.

Trauma-focused psychotherapy also shows some efficacy in the treatment of PTSD and is often the first-line intervention selected, given the known limitations in pharmacotherapy. Prolonged Exposure (PE) and Cognitive Processing Therapy (CPT) are gold standard treatments [10,11], but access to appropriately trained therapists is limited and the interventions are quite challenging for patients. The attrition rates range from 17% to 55.8% [12,13], and nonresponse can be as high as 50% [14]. Regardless of treatment modality, troubling symptoms often persist even in patients classified as responders.

Recently, placebo-controlled trials have demonstrated acute and enduring therapeutic effects in PTSD, after administration of two to three doses of 3,4-Methylenedioxymethamphetamine (MDMA) with manualized psychotherapy [15-18]. These robust enduring clinical effects were recently replicated in a Phase 3 trial [19]; a second Phase 3 trial is underway, and a favorable clinical outcome could place MDMA-assisted psychotherapy on track for FDA approval.

3,4-methylenedioxy-N-methylcathinone (methylone; also known as MDMC, βk-MDMA, and M1) is a Rapid Acting Empathogen (RAE) structurally related to MDMA. A recent observational study compared the acute pharmacological and physiological effects of orally administered methylone and MDMA in healthy participants with a history of prior exposure to both compounds. While they are structurally similar, methylone produced less intense psychostimulant and empathogenic effects, including lessened euphoria, inebriation, stimulant-like effects, and changes in cognitive and body perception, with increased sociability relative to MDMA [20]. The shorter and milder pharmacological effects could be explained in part, by differences in serotonin (5-HT) receptor affinity [21-24].

Case Presentation

Methods

Archival clinical data were obtained from 21 patients with a primary diagnosis of PTSD who received one or more oral methylone administrations as part of specialty care in an outpatient psychiatric setting. This retrospective case series was reviewed and determined exempt from IRB approval by WCG IRB. No protected health information was disclosed and no consent was obtained from patients for the use of their data. Data was systematically compiled from information collected as part of routine clinical work. Diagnoses were confirmed by an experienced clinician using semi-structured interviews. Baseline symptom severity and symptom improvement were evaluated using the Clinical Global Impressions Scale-Severity (CGI-S) and Clinical Global Impressions Scale-Improvement (CGI-I) respectively. Patients were evaluated for observed or reported safety events following dosing sessions. Follow-up varied, ranging from one week (Case 1) to 15 years (Case 15).

Results

Methylone produced acute and enduring improvements in PTSD symptoms, without any notable lasting adverse effects. Clinical data are presented in Table 1. Twelve patients (57%) were female; 19 (90%) were white and a mean age of 47.6 (range: 25 to 78). Baseline CGI-S scores ranged between 4 and 7 (i.e., moderately to severely ill; Figure 1). Six patients (28.6%) were on concomitant SSRI or other psychotropic therapy at the time of methylone dosing. Prior or current therapies included: SSRIs/SNRIs (n=14; 66.7%), supportive unstructured therapy (n=8; 38%), structured cognitive behavioral therapy (n=4; 19%), and unspecified antidepressant pharmacotherapy (n=3; 14.3%).

All patients achieved at least minimal improvement (CGI-I 1, 2 or 3) following treatment, with 17 achieving "much" or "very much improved" ratings (Figure 1). This trend was observed even for patients who received only a single dose of methylone (n=9), where 8 patients (89%) achieved CGI-I scores of 1 or 2. For patients with multiple methylone dosing sessions (n=12), initial improvement was noted after the first session in 83% (n=10) of patients.

Information on durability of clinical effects was captured for 17 patients. One individual reported no durable effect (i.e., reported acute improvement in symptom severity yet returned to baseline almost immediately following the sessions), and 16 reported a durable effect (>six months in 11 patients) and one patient each reported a sustained effect of three months, two months, and one week respectively. Of note, one patient's information was noted as, "no longer qualified for the disease (i.e., PTSD)" following the 4th methylone dosing session as determined by the treatment team. It is not known how long this remission was sustained.

Dosing summary

Methylone was administered orally and concomitant medications were not changed, halted, or tapered. In many cases, an additional "booster" dose of methylone was administered 1 h after the initial dose to extend the therapeutic window and optimize clinical response. Booster doses were included for 19 patients in at least one session. Starting doses were between 100 mg and 270 mg. These as well as booster doses were selected based on clinical judgment.

Safety

Methylone was well tolerated, and no patients discontinued treatment due to adverse events. A total of four adverse events were noted in three patients; none were considered severe, and none required medical intervention. A 75-year-old male developed lightheadedness around the end of his fifth session, at a total dose of 300 mg (150 mg followed by booster dose of 150 mg, the highest dose administered for this patient). This symptom resolved quickly, and the individual was feeling well upon discharge with no other adverse effects. A 70-year-old male administered methylone 690 mg during a single dosing session (200 mg followed by booster doses of 250 mg and 240 mg) did not experience any adverse events during the session but reported sleeplessness and loss of appetite the night following the session with resolution the following day. A 78-year-old male reported a flashback-like experience during one of 5 dosing sessions with a total methylone dose at each session ranging from 100 mg to 300 mg.

Discussion

In this case series of patients with PTSD, methylone produced

Table 1: Demographic data, clinical characteristics, and response to treatment.

ID	Age (years)/ Sex (M/F)	Comorbidities	Prior Treatments	Concomitant Medications	Total Methylone Dose Range Across all Sessions (mg)	# Observed Dosing Sessions	Treatment Duration	Baseline CGI-S	Peak CGI-I (Time since baseline CGI-S)
1	62/M	Bipolar II; GAD; SCZ; Insomnia; SI	Psychotherapy; psychiatric therapy; olanzapine; quetiapine; venlafaxine; opiates	lamotrigine; lurasidone HCl; clonazepam; amphetamine, dextro-amphetamine; propranolol	550	1	1 session	7	1 (1 week)
2	75/M	Parkinson's Disease; Cardiovascular diagnosis; Atrial fibrillation; Pacemaker	CBT, Breath work, hypnosis, unspecified SSRIs		100 to 300	5	>18 months	5	1 (11 months)
3	49/M	MDD; GAD; Social phobia; SI; Insomnia	Talk therapy; CBT; experiential therapy (ketamine); fluoxetine		250 to 620	4	10 months	7	1 (10 months)
4	54/M	Eating disorder (UNSP); Insomnia	Talk therapy; CBT; support group; SSRI (escitalopram)	escitalopram	150 to 350	3	11 months	5	3 (11 months)
5	38/F	MDD; BPD; SI	Residential clinical therapy including group therapy; breath therapy; talk therapy		400 to 500	4	2 years	6	1 (16 months)
6	52/F	GAD	~5 years talk therapy 2 experiential treatment search lasting 4 weeks (hug and scream + primal therapy)		150 to 410	6	1-2 months	5	1 (1 month)
7	46/F	N/A	Unspecified SSRIs		230	1	1 session	4	2 (1st session)
8	25/F	MDD; GAD; SI	Fluoxetine <60 mg		360	1	1 session	6	1 (1st session)
9	70/M	MDD	Unspecified SSRIs		690	1	1 session	5	2 (1st session
10	33/F	MDD;GAD; binge eating disorder; SI	Talk therapy; CBT; holotropic breath work; somatic experiencing; inpatient treatment; unspecified SSRIs	fluoxetine	310 to 460	3	5 months	6	1 (5 months)
11	78/M	UNSP anxiety disorder; Insomnia	Unspecified antidepressants	bupropion* lamotrigine	100 to 300	5	2 years	5	2 (2 months)
12	40/M	MDD; anxiety disorder; SI; Insomnia	Wellbutrin; unspecified SSRIs, psychotropics and unspecified narcoleptic	Unspecified SSRI	330	1	1 session	5	2 (1st session)
13	36/F	Insomnia	Unspecified sleep medication		220	1	1 session	5	1 (1st session)
14	38/F	Substance addiction; SI; insomnia	Detox for alcohol and narcotic abuse; couples counseling; unspecified SSRIs		470	1	1 session	6	2 (1st session)
15	28/M	MDD; UNSP Personality disorder	Holotropic breath work; weekly therapy; unspecified SSRIs		310 to 1020	unknown	3 years with a gap of 15 years, then 2 years	6	3 (2-3 days after each session, but relapsed soon after)
16	38/F	N/A	Unspecified SSRIs		300 to 330	12+	1.5-2 years	4	3 (after 10 sessions, >1 year)
17	25/M	N/A		Unspecified psychotropic	150	1	1 session	5	3 (1st session)
18	58/F	MDD; UNSP anxiety	Several inpatient treatments; weekly therapy sessions; unspecified SSRI combination therapy		250 to 400	5	10 months	5	2 (8 months)
19	59/F	MDD	Talk therapy; meditation, unspecified SSRIs, recreational psychedelics		180 to 400	3	9 months	5	1 (9 months)
20	58/F	MDD;UNSP anxiety; social phobia; SI	Prior inpatient treatment; multiple psychiatric modalities; Multiple medications		100	1	1 session	7	2 (1st session)
21	38/F	N/A	Inpatient treatment; unspecified SSRI		250 to 360	4	3.5 years	5	2 (1 year)

*__Case 11:__ Based on the case narrative, it is unknown if bupropion was aprioror concomitant medication

Abbreviations: BPD: Borderline Personality Disorder; CBT: Cognitive Behavioral Therapy; F: Female; GAD: Generalized Anxiety Disorder; M: Male; MDD: Major Depressive Disorder; NR: Not Reported; PTSD: Posttraumatic Stress Disorder; SCZ: Schizophrenia; SSRI: Selective Serotonin Reuptake Inhibitor; SNRI: Serotonin-Norepinephrine Reuptake Inhibitor; SI: Suicidal Ideation; UNSP: Unspecified

Notes: The precise modalities and differences between prior therapies (talk therapy, CBT, psychotherapy, etc.) were not described in the case narratives and are reproduced here as written in the chart materials

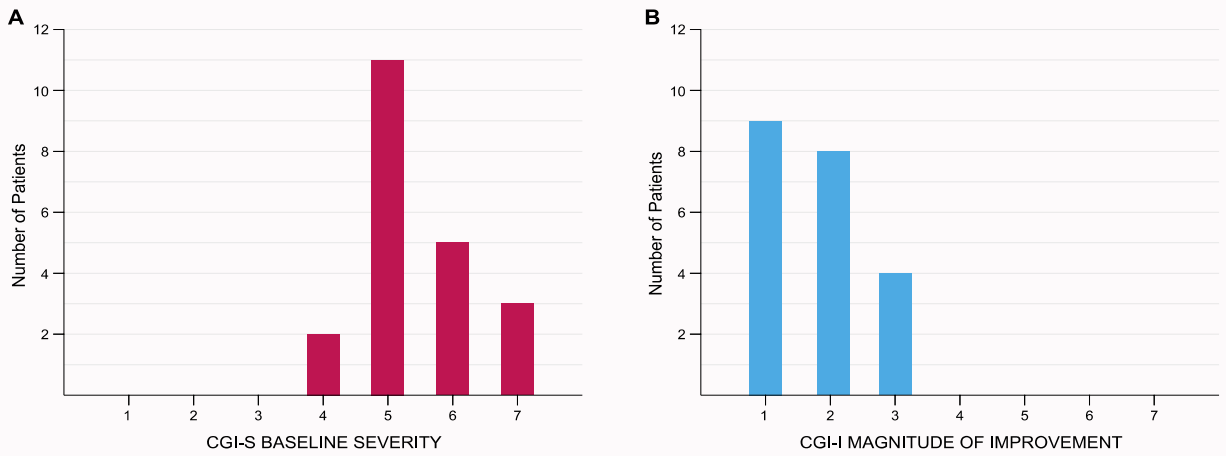

Figure 1: Baseline symptom severity and magnitude of improvement following methylone dosing.
CGI-S: Clinical Global Impressions-Severity, where the higher the score the greater the severity of symptoms; CGI-I: Clinical Global Impressions-Improvement, where the lower the score the greater the magnitude of improvement

rapid symptom improvement, as measured by CGI-I. The majority (90%) had baseline CGI-S of 5 or greater ("markedly" or "severely" ill), with 3 patients in the category of CGI-S of 7 (i.e., amongst the "most severely ill patients"). The majority (81%) of patients achieved scores per CGI-I corresponding to "much improved" or "very much improved". These therapeutic effects are similar to those seen in recent controlled clinical trials of MDMA in conjunction with manualized psychotherapy for PTSD, in which rapid and robust improvements were observed in severely ill, complex, and treatment-resistant patients [19].

Methylone was well-tolerated over a broad dose range (100 mg to 1020 mg), with one to ten administrations. Adverse events were reported only in three older patients, age 70 and over; these were mild and required no intervention. Notably, none of these adverse events occurred in patients receiving concomitant SSRI therapy, which is noteworthy as MDMA trials have required patients to taper off of these medications. The preliminary results summarized for this case series warrants further investigation of methylone as a potential treatment for PTSD.

Strengths and Limitations

This is the first report of methylone administration in patients with PTSD. This case series provides encouraging initial evidence that methylone may have utility in the pharmacological treatment of PTSD. These findings have limitations. Participants were treated clinically; data for this report were collected retrospectively from review of clinical records. Dosing and follow-up were variable and there was no randomization, control, or blinding to treatment condition. It would be premature to draw conclusions regarding optimal dosage and duration of treatment from this preliminary report. Further, the sample lacks diversity. Despite these limitations, this data from a complex patient population constitutes the first clinical evidence for the efficacy of methylone in the treatment of PTSD. Strength of this preliminary report is the complexity of the sample, which aids in generalizability. Prospective well-controlled studies in larger and more diverse samples will be required to clarify the benefits and side effects of methylone and to optimize the dosing and strategies.

Methylone has not received the same cultural or clinical attention as MDMA, perhaps due to its milder and shorter psychopharmacological effects (e.g., stimulant, euphoric, empathogenic effects). However, these "softer" effects may be helpful for some patients who are not appropriate for treatment with the more intense acute psychological and physiological effects of MDMA. If future research supports the conclusion that methylone can produce rapid-acting and robust symptom improvement in treatment refractory PTSD, it may prove to be an important and urgently needed addition to the therapeutic armamentarium.

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Disclaimer

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Declarations of Interest

Declaration of Interest/Funding: Dr. Kelmendi is a Co-founder, advisor, and has equity in Transcend Therapeutics and is also a consultant for Ceruvia Lifesciences. Dr. Pittenger serves as a consultant for Biohaven, Teva, Lundbeck, Brainsway, Ceruvia Lifesciences, Transcend Therapeutics, and Freedom Biotech, receives royalties and/or honoraria from Oxford University Press and Elsevier. He is PI for a sponsored preclinical research study funded by Transcend Therapeutics. Dr. Stogniew is an employee and has equity in Transcend Therapeutics. Mr. Mandell is an employee and has equity in Transcend Therapeutics. Dr. Seelig has served as a consultant for Transcend Therapeutics. Dr. Averill has served as a consultant, speaker and/or advisory board member for Guidepoint, Transcend Therapeutics, Source Research Foundation, Reason for Hope, and Ampelis.

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