Effects of 3,4-Methylenedioxymethamphetamine on Patient Utterances in a Psychotherapeutic Setting

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Abstract: 3,4-Methylenedioxymethamphetamine (MDMA) administered as an adjunct to talk therapy influences patient speech content and increases improvement in treatment-resistant posttraumatic stress disorder (PTSD). Data came from the recordings of Mithoefer et al. (2011). In the third therapeutic session studied, patients were assigned, double blind, to an MDMA or a placebo group. Condition-blind scorers listened to therapy recordings and scored utterances where patients initiated topics that were empathic (regarding others' emotions), entactic (requesting or appreciating physical touch), or ensuic (describing a change in their sense of themselves). Patients who received MDMA produced high levels of ensuic, empathic, and entactic utterances compared with those who received the placebo. Interrater discourse scoring was reliable. The relationship between the number of scored utterances and the Clinician Administered PTSD Scale scores measuring PTSD severity after the treatment was significant, and reanalysis grouped bimodally into "many" or "few" such utterances remained significant. MDMA assisted these patients in having meaningful and disorder-resolving thoughts and discourse in talk therapy.

Key Words: PTSD, MDMA, talk therapy, patient utterances

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Posttraumatic stress disorder (PTSD) is a relatively common mental illness. PTSD occurs in response to a traumatic event and includes symptoms such as reexperiencing, avoiding associated activities, and hypervigilance. About 10% (Breslau, 2001) of the population is estimated to be affected during one's lifetime. Motor vehicle accidents and sexual assault (Norris, 1992) are the leading causes of PTSD in America. Worldwide, warfare expands the rate of PTSD and also contributes to difficulty in assigning the diagnosis (Taubman-Ben-Ari et al., 2001). Even with diagnosis and attempted treatment, many of those who experience trauma do not improve (Frueh et al., 1994), and left untreated, it can persist for decades (Markowitzh, 2007).

Psychotherapy for PTSD includes a variety of theoretical models (Taylor et al., 2003), as well as inevitable differences among practitioners. In Taylor's meta-analysis, clinically significant outcomes (2 standard deviations of reduction in symptoms) ranged from 27% to 73%, depending on the symptom and the class of treatment (exposure, relaxation, and eye movement desensitization and reprocessing). Posttreatment tests found sustained health, where patients no longer met the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (American Psychiatric Association, 1994), criteria for PTSD, in about 30% to 80% of their participants. Foa et al. (2006) assigned 90 female assault survivors to one of three types of follow-up (brief cognitive behavioral therapy, supportive counseling, or assessment condition). At the longest available follow-up (mean, 9 months), all conditions had approximately the same level of effect: the disorder persisted in about 30% of patients in each type.

PTSD has a great breadth of effects on the brain's morphology and activity (Shin et al., 2006) and its neurochemical metabolism (Karl and Werner, 2010). A wide variety of medications have been used to treat it. Chavez (2006) reviewed a range of approaches, including the beta-blocker propranolol as "secondary prevention" between trauma and potential PTSD development. The current first-line approach is treatment with selective serotonin reuptake inhibitors (sertraline and paroxetine are Food and Drug Administration [FDA] approved), atypical antipsychotics for particular symptoms, other antidepressants for those who cannot tolerate or do not respond to the first-line group, and anticonvulsants.

Both psychotherapy and pharmacotherapy have pitfalls. The search for an individual's treatment can be expensive and time consuming; undesirable effects such as disruptions of appetite and sleep are common. Psychotherapy may be ineffective, and review of traumatic events may even be further traumatizing, depending on social context (*e.g.*, Brounéus, 2008). Pharmacotherapy is typically continuous; although symptoms may be controlled, the disorder persists, leaving the patient more vulnerable to future illnesses (Boscarino, 2008).

One promising combination has a long history of anecdotal reports but has received little systematic testing. This involves the administration of the monoamine releaser 3,4-methylenedioxymethamphetamine (MDMA) during a long session of psychotherapy. The rationale is that MDMA's acute effects support the kind of psychological changes that can heal the damage of PTSD. In one study of MDMA's prosocial effects in humans, Harris et al. (2002) administered a single dose (at three quantitative conditions) to MDMA-experienced volunteers and examined physiological, hormonal, and subjective effects. They reported that MDMA increased insight, confidence, and closeness to others, which could aid in psychotherapy. Before MDMA's listing in Schedule I of the Controlled Substances Act in 1986, a number of psychotherapists used this approach. During the 1985 to 1986 Drug Enforcement Administration Administrative Law hearings on MDMA, several doctors reported hundreds of examples of such use, with benefits such as increased therapeutic alliance and accelerated healing (*e.g.*, Greer and Tolbert, 1986), although few or no rigorous analyses were performed. In 1986, Drug Enforcement Administration Administrative Law Judge Francis Young issued the opinion that MDMA should be placed in Schedule III; this was overruled on the grounds that it was not FDA approved.

In 2002, the FDA cleared a phase 2 trial of MDMA-assisted psychotherapy for treatment-resistant PTSD, proposed by Mithoefer et al. The study was reviewed and approved by the Copernicus Group Institutional Review Board, Research Triangle Park, NC, and participant enrollment began in 2004. Double-blind administration of MDMA or placebo (lactose) occurred in one to three sessions of surrounding talk therapy. Conclusions were published by Mithoefer et al. (2011).

This analysis takes a novel perspective by simultaneously analyzing psychotherapy, psychopharmacology, and discourse-level linguistics. It examines subjects' initiation of discourse topics in the first psychotherapeutic session using MDMA or placebo from Mithoefer et al. (2011). Only audio recordings of adequate quality (a total of 20) were used. Recordings were obtained through the data library of the Multidisciplinary Association for Psychedelic Studies.

Previously documented effects of MDMA qualified it as an "empathogen" (meaning "a substance that increases interest in others'

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feelings") and/or "entactogen" (derived from the Greek root "touching within," but used here to define a substance that increases interest in or appreciation of touch). There has been some controversy over which name should be used to describe a given set of substances (1,3-Benzodioxolyl-N-methylbutanamine, 3,4-methylenedioxy-N-ethyl-amphetamine, and methylone, as well as MDMA) (Nichols, 1986; Nichols et al., 1993). For the purposes of this article, these terms will be used to describe the effects of MDMA on topics of discourse—expressions of interest in others' emotions or touch—rather than drug categories.

Topic initiations of other people's feelings (typically the therapists') or of a desire for or pleasure in touch were marked as "empathic" or "entactic," respectively. Topics introduced by the therapists were not included. There were also a number of very striking utterances in which a change in the subject's sense of self appeared. They occurred both in narrative formats and were announced as subjective experiences. These were also counted and labeled as "ensuic" (Corey, 2008). The Latin root *sui* means "of oneself," and an *ensuigen* is therefore a substance that brings out a sense of oneself.

METHODS

Participants and Setting

Participants in the MDMA-assisted psychotherapy study by Mithoefers et al. had Clinician Administered PTSD Scale (CAPS) (Blake et al., 1995) scores of 50 or higher, with PTSD resulting from crime or combat, and no major psychiatric disorders except affective disorders highly comorbid with PTSD. All subjects were white. Eighteen were women and five were men. The mean age was 40.5 years, the mean pretreatment CAPS score was 81.5, and the mean duration of preexperiment therapy was 62.4 months. Twenty subjects yielded useable recordings of the relevant visit and comprised the subject group for this article.

All subjects signed informed consent during the initial screening visit. Neurophysiological measures were made at the second visit, and then there were two 90-minute introductory sessions with the two cotherapists. The general therapeutic plan included approximately 22 visits in total, with one to three visits incorporating MDMA or a placebo. The therapeutic discourse style was supportive and nondirective. Sessions took place in a comfortable environment in which subjects could sit, stand, or lie down. Music and eyeshades were available, and subjects were encouraged to "go inside" and introspect silently at times as well as to converse with the therapists.

Study Design

Visit 5 was an all-day session typically including about 6 hours of psychotherapy. MDMA (125 mg) or placebo was administered, double blind, with a half-sized secondary dose offered after 2 hours. An emergency crash cart was available, and blood pressure and temperature were checked periodically. The subject spent the night in the clinic with a nurse on duty, had a 90-minute talk session with the therapists the next morning, and was allowed daily telephone contact for the following week. This provided a very extended conversational setting for the potential period of medication effects and their aftermath. CAPS scores were reassessed 4 days after the session. (Also later in the experiment, but we have used that day's score for our analyses.)

Recordings of visit 5, the first MDMA or placebo session, were chosen as the cleanest data source about the effects of the medication because the least accumulated effects of psychotherapy were expected then. The measurement of CAPS scores after 4 days, however, does include the effect of a conversational and supportive structure in which the drug therapy was embedded.

Recording quality was highly variable, and time stamping was inconsistent, but at least 2.5 hours of audio data was available and comprehensible for each subject included in this report. All sections of recordings were listened to and scored at least twice or multiple times when recording issues interfered with audio clarity. All data were deidentified.

Scoring and Interrater Reliability

A condition-blind scorer (the first author, a neuroscientist specializing in brain and language) listened to the session recordings and marked utterances where patients initiated empathic, entactic, or ensuic topics. The scorer was then unblinded to the condition, and mathematical relationships between the number of utterances and MDMA or placebo status were explored.

To test whether this finding revealed a skill peculiar to the first author, an undergraduate with no previous experience of discourse analysis or psychiatry was recruited to reanalyze the data. Training consisted of a single verbal conversation with the first author about utterance types, followed by independent scoring of a randomly selected single subject, followed by a review of that subject's data with the first author. The training subject's data were not counted in further statistical analyses.

RESULTS

Subjects who received MDMA produced many more scored utterances than subjects who received placebo. A two-tailed mid-p exact test yields a p value of 0.01; a two-tailed Fisher's exact test yields a p value of 0.02. Figure 1 illustrates each subject's exposure condition and the number of scored utterances. The total such utterances per subject were graphed and showed a bimodal distribution. The subjects were grouped into high and low utterance groups. The low group produced six or fewer scored utterances, and the high group produced nine or more; no subject produced seven or eight utterances.

A higher number of scored utterances also correlated with lower posttreatment CAPS scores by Pearson's r ($r = -0.506$, $p = 0.023$, $n = 20$). With utterances grouped into "many" and "few" bimodal categories, Pearson's r remained significant ($r = -0.596$, $p = 0.006$, $n = 20$). A higher number of scored utterances did not directly correlate with higher overall change in CAPS scores from pretreatment to posttreatment ($r = 0.305$, $p = 0.191$, $n = 20$). However, utterances grouped

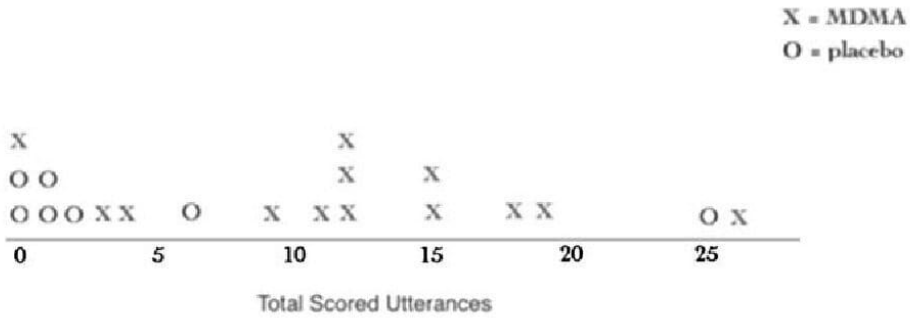

FIGURE 1. Total empathic, entactic, and ensuic utterances for each subject.

into "many" and "few" bimodal categories did correlate with the overall change in CAPS scores ($r = 0.513$, $p = 0.021$, $n = 20$).

Interrater Reliability

Overall, the less experienced scorer noted about 30% fewer empathic, ensuic, or entactic utterances than the first author did. However, the distribution was similarly bimodal. Scorers agreed on which subjects fell into the "low" or "high" utterance categories for 14 subjects and disagreed on 5, all of whom were considered "low" by the second scorer but "high" by the first. The raw interrater reliability score was 72%. A one-sided kappa test for interrater reliability compared with randomness yielded a value of 0.0124 ($p < 0.05$).

Both exposure conditions had atypical responders (included in these analyses), which warranted additional scrutiny.

Placebo Group

Some scorable utterances were found in the placebo subjects' data. Most belonged to a single outlier, who produced 20 ensuic and 5 empathic utterances. Among the other six placebo subjects, a total of five ensuic and two empathic utterances were scored, but no more than two in any single subject. No entactic utterances were made by any placebo subjects.

MDMA Group

Only one MDMA subject made no scorable utterances. The rest were roughly normally distributed between 3 and 26 utterances, with a mode at 12. Again, ensuic topics predominated. Empathic statements occurred more often in proportion to the ensuic ones than in the control group. Entactic utterances also appeared in contrast to the controls.

Example Utterances

Here are utterances by the MDMA subjects from the median quartile, representing entactic, empathic, and ensuic topic initiations:

"I did not choose consciously to dissociate. It was the dissociation I resented itself" (ensuic).

"I love that feeling of like all this stuff is in you—look how neat, look how marvelous you are. It's such a nice feeling after spending 99% of your life going I'm shit. What I want is to make the leap from that feeling now to like all the time" (ensuic).

"It feels nice, you holding my hand" (entactic).

"I was worried about you guys at first, cause I was like oh they must be so bored" (empathic).

"Contact feels nice too" (entactic).

"I was thinking it felt nice to hold your hand" (entactic).

"I hope you guys don't want to go because I want to stay here a little bit" (empathic).

"Half my life I've, pharmaceuticals, and it's never been, it's never worked. I mean sometimes I've been able to balance my checkbook. But that's about it, that's about as far as it's gotten me in healing. But this is like, just to know this stuff's in there is just like a huge for me, it's just a huge thing" (ensuic).

"So all that clutter and that clatter is because you think you did something wrong. And then you want to fix yourself and change yourself. And so you always are working on yourself when it's not really you that did anything to cause that. And you can only work on yourself so much" (ensuic).

"I mean I knew that logically but I just hadn't connected with it" (ensuic).

"So I guess what I was trying to do wasn't what I needed" (ensuic).

"I've always heard from people that I don't know that have [taken MDMA] that they're all over each other like I love you, you're so great, I love you. And I haven't really felt that desire to tell you I love you, you're so great, or I love you you're so great. I haven't really felt that desire. Except maybe to tell me that I love me" (ensuic, not empathic).

"It's like there's no ropes tying around me. I can feel them loosening" (ensuic).

DISCUSSION

Ensuic utterances, in which speakers describe a change in their sense of themselves, might be considered a hallmark of successful talk therapy. All such utterances recorded in this study were positive and appropriate to the goal of recovery from PTSD. Empathic utterances seem to indicate increased interest in the feelings of other people present. Such effects might be particularly relevant in couple or family therapy or in cases where there is difficulty forming a bond between patient and treatment providers. Entactic utterances, which were only found in the MDMA data, may indicate increased attention or sensitivity to tactile stimuli, and/or physical discomfort from MDMA. A relationship to the therapists allowing supportive touch as well as talk may help. This study may underestimate tactile interactions, because data were solely audio recordings and touch may not include verbalization. The analysis demonstrates that the presence of MDMA significantly increases the quantity of ensuic, empathic, and entactic topic initiation utterances in a group of subjects with treatment-resistant PTSD. Such utterances appear to reflect cognitive processes important to improvement in the participants' mental health, as shown by their posttreatment CAPS scores.

Atypical Responders

Three MDMA-receiving subjects fell into the "low" category for scored utterances: one each at zero, three, and four utterances. Here are the scored utterances for the two who made any scorable statements.

Subject A:

"I felt that inner connection between me and [partner] that I haven't felt in a long time you know that connection that's just been missing. That and the kids it's just the same thing with them too" (empathic).

"So it's not just about the rape, it's not just about any one thing. It's so many different things and I really think this was just the straw that broke the camel's back" (ensuic).

"All these things that I should be feeling that I have not allowed myself to feel, all these things that I have now that I've wanted the great husband and all that, depersonalization gets worse it's like signaling me, saying hey yoo-hoo. That makes sense; actually it does. Maybe I was just looking at it all wrong" (ensuic).

Subject B:

> *"Can I tell you something? Really? It's not going to mess things up?" (empathic).*
>
> *"I don't feel at home in my whole life" (ensuic).*
>
> *"I'm afraid you'll think I'm nutty that I don't feel at home in this country" (empathic).*
>
> *"I didn't want you to think I was talking out my ass when I said I was pretty good" (empathic).*

Subject A, above, when asked, said he or she thought that he or she had received MDMA. Subject B was not asked this question during recording.

One placebo recipient generated an exceptionally large number of scored utterances (25 total: 5 empathic, 0 entactic, and 20 ensuic). The therapists may have suspected this session of being a control (the scorer did) because her blood pressure never rose as is typical for MDMA (a design element that might have adversely affected the blind). However, her feelings of relationship to the therapists and of transformation in her sense of herself was considerable, as demonstrated in her speech:

> *"I feel more connected" (ensuic).*
>
> *"But I kept thinking you were there" (empathic).*
>
> *"I didn't know what I lost […] I lost my voice. That's what I lost" (ensuic).*
>
> *"Yeah, I just feel different. Feel different from you. Feel different from me" (ensuic).*
>
> *"You feel like you're there" (empathic).*
>
> *"I was just trying to control the situation. It was so dumb, why did I even do it? It was so much effort" (ensuic).*
>
> *"I got it, I got it, I got it. It's not important for me to think about [the trauma] anymore. It's important for me just to think about me" (ensuic).*
>
> *When asked if she thought she had received MDMA, she said, "I thought no."*

Although atypical, this subject's existence is unsurprising; talk therapy is often useful in resolving PTSD. This subject's previous treatment resistance may have been due to poorer connections to previous therapists, judging from her particular speech content. Perhaps other features of the therapy, such as the music or the all-day nature of the session, also made a difference. As the single high-scoring individual among the seven examined controls, this case contributed less to the group differences than the presence or absence of MDMA. However, also note that she was the only placebo patient who entered the study with PTSD and left without it, as defined by a CAPS score lower or higher than 50. Her CAPS scores were 54 at entry, 21 at two visits after this experimental one, and 15 at the end of the therapy with the Mithoefers. Her utterances resembled the responders in the MDMA condition, possibly reflecting analogous mental processes.

In turn, consider the 3 of 12 MDMA subjects who showed no significant improvement after either the first drug session or the full treatment. One subject's CAPS scores were 43/58/46 (pretreatment/post–visit 5/posttreatment) with 19 scored utterances, another one's scores were 65/70/29 with four scored utterances, and those of the last were 102/47/60 with 12 utterances, possibly representing three different types of responses to the therapy. The first subject's PTSD symptoms, and thus the CAPS score, may be related to a comorbid issue that cannot be addressed by treatment aimed at improving PTSD. Scores of 43 pretreatment and 46 posttreatment are below the CAPS score inclusion criteria of 50. The first MDMA session, focusing on something that was not "really what the problem was," may have increased their trauma-related difficulties. For the second, it is possible that the first treatment similarly increased their sensitivity to their, perhaps previously relatively well-managed, trauma and that the rest of the treatments—the second MDMA session and the many sessions of unmedicated therapeutic talk—were necessary for their recovery. The third patient was in the top quartile of CAPS scorers pretreatment, and his or her improvement was extremely significant (reduction of ≥15 points in the CAPS score); the patient may simply need more therapy than what this experiment provided to recover fully.

MDMA as a Therapeutic Agent

Based on this analysis, improvement of PTSD symptoms was related to crossing a threshold in production of scorable utterances, as opposed to the precise number of such statements. At this visit, early in the therapeutic process, patients who received MDMA were substantially more likely to fall into the "high" utterances category and show reduction in their CAPS scores than were patients receiving placebo.

The roughly normal distribution of utterances for experimental subjects in Figure 1 suggests individual differences in response to a standardized single dose. If other physiological parameters (such as blood pressure) are within appropriate limits, it may be useful to adjust dosages for outlying responders if another MDMA session is planned. However, as with the controls, it is also most important to determine whether the subject is currently in a situation suitable for recovery or this would interfere with an adaptive response to an ongoing threat. In each case, utterances should be examined individually. In the case of subject A above, the utterances appear to be on healing themes and, despite their relative scarcity, may represent therapeutic progress. Subject B's speech, however, indicates fear of the therapists' potential reactions, although their introduction of the therapists' states of mind as a topic for discussion indicates empathic thinking as scored in this study; it may be necessary to examine subject B's life context for barriers to therapeutic alliance. In the case of the subject who made no scorable utterances, if other indications allow, it may be useful to increase the dose.

The integration of new feelings provides a good example for why MDMA must be considered as only one element of this model of treatment. Even if a patient experiences improvement while affected by a substance, he/she must still integrate these new feelings with his/her usual modes of thinking to achieve optimal long-term health. Any treatment effect may disappear if longer-term support is not provided (Doblin, 1998). A recovery that is endogenously maintained is a healthier outcome than a transient feeling while medicated, and this is at least as true of episodic chemical interventions as of the presently more common daily pill regimens. MDMA does not stand alone in this therapy: it is part of a discourse relationship.

Medical care is also part of the relationship. No adverse effects on cognition were found in testing after the full course of treatment, nor were there any serious adverse events during the sessions. Mild adverse events, such as feeling chilled, were common; these were generally resolved during the session, for example, by providing a blanket. Occasional inpatient, physician-attended drug sessions are safer than ongoing, patient-managed, single or several times daily drug regimens, allowing for better recognition and support of adverse events.

In terms of patient response, MDMA-assisted psychotherapy appears to be a very effective aid in recovery from treatment-resistant PTSD. Patient utterances, regardless of MDMA or placebo, are similarly strong predictors.

Very little research into entactogenic or empathogenic (let alone ensuigenic) substance use within therapy has been practicable, primarily

because of political restriction in conducting clinical trials. The encouraging results of this study should serve as a launching point for future research. MDMA's characteristics may indicate therapeutic usefulness for more disorders that affect conversation in relationships, for example, borderline personality disorder or autism, or in family therapy. Other compounds with similar qualities may prove to be even more effective as therapeutic agents, but equally rigorous placebo-controlled or substance-comparative studies would be required. However politically challenging it may be to run these studies, public health should be the challenge of greatest priority for medical research.

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DISCLOSURE

The authors declare no conflict of interest.

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