MDMA-Assisted Psychotherapy Using Low Doses in a Small Sample of Women with Chronic Posttraumatic Stress Disorder†

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Abstract—The purpose of this study was to investigate the safety of different doses of MDMA-assisted psychotherapy administered in a psychotherapeutic setting to women with chronic PTSD secondary to a sexual assault, and also to obtain preliminary data regarding efficacy. Although this study was originally planned to include 29 subjects, political pressures led to the closing of the study before it could be finished, at which time only six subjects had been treated. Preliminary results from those six subjects are presented here. We found that low doses of MDMA (between 50 and 75 mg) were both psychologically and physiologically safe for all the subjects. Future studies in larger samples and using larger doses are needed in order to further clarify the safety and efficacy of MDMA in the clinical setting in subjects with PTSD.

Keywords—MDMA, MDMA psychotherapy, posttraumatic stress disorder, PTSD, safety

3,4-Methylenedioxymethamphetamine (MDMA, "Ecstasy") is a ring-substituted phenethylamine with a chemical structure related both to mescaline and methamphetamine. MDMA possesses a distinctive and unique psychological profile characterized by a specificity to act over the human emotional sphere (Shulgin & Nichols 1978) without notably affecting other psychological functions, such as visual perception or cognitive process (Harris et al. 2002; Tancer & Johanson 2001; Cami et al. 2000; Vollenweider et al. 1998). Because of this unusual quality, a new pharmacological category,

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entactogens, has been established to denote MDMA and some other chemically-related compounds (Hermle et al. 1993; Nichols 1986).

MDMA was first synthesized by the pharmaceutical company Merck in 1912 as a precursor of a haemostatic drug called methylhydrastinin, but it was not tested at that time either in humans or animals (Freudenmann, Öxler & Bernschneider-Reif 2006). In the 1950s, the U.S. army assayed a number of phenethylamines, including MDMA, in toxicological animal studies (Hardman, Haavik, & Seevers 1973) but there are no references regarding its use in military human experiments. This research remained secret until publication in 1973. At the beginning of the 1970s, the former Bureau of Narcotics and Dangerous Drugs (now the Drug Enforcement Administration—DEA) found MDMA for the first time being used on the street (Gaston & Rasmussen 1972) but the first scientific references regarding its pharmacological profile did not appear until the end of that decade (Anderson et al. 1978; Shulgin & Nichols 1978), some years after its rediscovery by the chemist Alexander Shulgin (Shulgin & Shulgin 1991).

From the rediscovery of MDMA until its prohibition in the U.S. in 1985, MDMA was widely used as an adjunct to the psychotherapeutic process (Grinspoon & Bakalar 1986), although no formal controlled studies were undertaken. It has been estimated that during this period around 500,000 doses of MDMA were administered in psychotherapeutic settings (Rosenbaum & Doblin 1991) and that about 4,000 people were introduced to the therapeutic use of MDMA just by Leo Zeff, Ph.D., the "Secret Chief" and leader of the underground therapeutic use of MDMA, (Stolaroff 1997; Shulgin & Shulgin 1991).

The inclusion of MDMA in the list of Schedule I controlled substances shut down all legal use, though in recent years there is a resurgence in the scientific investigation of the psychotherapeutic potential of MDMA (Check 2004; Doblin 2002), with studies investigating MDMA-assisted psychotherapy in subjects with PTSD approved in the U.S., Switzerland and Israel and one study at Harvard Medical School approved to investigate MDMA-assisted psychotherapy in subjects with anxiety associated with advanced-stage cancer patients (Allen 2006).

Before the prohibition of MDMA in 1985, it was used by a wide range of psychotherapists to treat diverse psychological disorders, including psychosis and anxiety, in individuals and couple therapy as well in group therapy (Grinspoon & Bakalar 1986; Greer 1985). MDMA was also useful in reducing physical pain secondary to some kinds of cancer (Greer & Tolbert 1998). Most clinicians agreed that it was most useful in the treatment of sequelae secondary to psychological trauma, such as child abuse or war stress (Greer 1985). The only quantitative data regarding the efficacy of MDMA were provided by Greer & Tolbert (1998, 1990, 1986) in their publications describing MDMA-assisted psychotherapy in 80 patients. Greer and Tolbert found that 90% of their patients reported positive experiences with lasting beneficial effects that remained at the one-year follow-up. Of those 90%, one third had experienced just one dose of MDMA, another third had experienced two doses, and the last third had taken more than two doses. In a follow-up utilizing a self-report questionnaire mailed to 171 patients treated by psychiatrists with MDMA and/or LSD-assisted psychotherapy in Switzerland between 1988 and 1993 (121 or 71% of questionnaires were returned with data), Gasser (1996, 1995) found that 65% of these respondents reported "good improvement" and 26% "slight improvement" after a course of LSD or MDMA-assisted therapy. Treatment consisted on average of three years of therapy with 70 nondrug sessions and seven sessions with MDMA or LSD. Anecdotal accounts of MDMA-assisted therapy exist in print and in other media, including documents and testimony at the hearings on the scheduling of MDMA (www.maps.org/dea-mdma; Greer & Tolbert 1998; Grinspoon & Bakalar 1986; Wolfson 1986). Lastly, psychotherapeutic models using MDMA as an adjunct to the psychotherapeutic process in the treatment of depression (Riedlinger & Montagne 2001; Riedlinger & Riedlinger 1994), schizophrenia (Holland 2001), and posttraumatic stress disorder (PTSD) (Bouso 2001) have been proposed.

The therapeutic potential of MDMA consists in temporarily reducing or eliminating anxiety and fear, thus helping subjects gain access to their emotions and internal conflicts without the overwhelming fear normally associated with these emotions and memories. This ameliorative effect simultaneously helps subjects access these traumatic emotions and communicate them to a therapist, thus enhancing both the therapeutic alliance and the psychotherapeutic process (Greer & Tolbert 1998; Grinspoon & Bakalar 1986; Greer 1985). Since it enhances both introspection and the strength of the therapeutic alliance—the most important variables predicting therapeutic outcome (Alexander & Luborsky 1986)—MDMA seems an ideal tool for use in the psychotherapeutic process, especially for the treatment of PTSD (Bouso 2001). This article presents preliminary data from the first government-approved clinical trial designed to assess the safety and efficacy of MDMA in the treatment of PTSD. This study was approved by the Ethics Committee of the University Hospital "La Paz" and by the Spanish Ministry of Health. Although the approved protocol anticipated the participation of 29 women with chronic PTSD secondary to a sexual assault in the first phase, a series of political decisions as a result of favorable media coverage, and unrelated to any scientific or ethical considerations, led to the sudden discontinuation of the study (Caudevilla 2006, 2003; Bouso 2003; Bouso & Gómez-Jarabo 2003; Doblin 2002) when only six subjects had been treated. Data from those six subjects who took part in the study are presented and discussed below.

MATERIALS AND METHODS

Sample

The study enrolled six women with chronic, treatment-resistant PTSD, recruited in the years 2000-2002 through women's associations in the city of Madrid. They were between 29 and 49 years old, weighed between 50 and 61.3 kg and had no previous experience with MDMA. All subjects were in good physical health, confirmed by medical history, laboratory tests, ECG, and urinalysis, and had no other psychiatric disorder (except for PTSD and comorbid symptoms), as assessed by the structured psychiatric interview for the DSM-IV (Spitzer et al. 1995). Subjects had previously failed to respond to at least one standard treatment and were free of medications for at least one month before the beginning of the study. All subjects had to have negative pregnancy tests just prior to the drug administration session.

Study Design

The study was originally designed to assess the safety of a single dose of MDMA in women with chronic PTSD secondary to a sexual assault. It was planned to study five increasing doses of MDMA, ranging from 50 to 150 mg, in 29 women assigned to five different groups. Doses were selected based on previous psychotherapeutic (Greer & Tolbert 1986) and pharmacological (Cami et al. 2000) studies. The study design was a double-blind, ascending-dose study, randomized and placebo-controlled within each dose condition. Subject assignment to successive MDMA dose conditions occurred only after all subjects for the previous MDMA dose condition completed the experimental sessions. Groups 1 (group of 50 mg) and 5 (group of 150 mg) were composed of four subjects each, three receiving the MDMA dose and one receiving a placebo dose. Groups 2 (group of 75 mg), 3 (group of 100 mg) and 4 (group of 125 mg) were composed of seven subjects each, with five women receiving the MDMA dose and two women the placebo in each group. In this way, we planned to have 21 subjects receiving an MDMA dose and eight subjects receiving a placebo, allowing us to compare across doses and between drug and placebo. As mentioned above, the study was suddenly shut down as a result of political pressure when only six subjects had been treated. The data presented here were gathered from those six subjects: subject 2 and 6 received placebo; subject 1, 3 and 4 received a 50 mg dose of MDMA; and subject 5 received a dose of 75 mg of MDMA.

All subjects had six nondrug psychotherapy sessions with two therapists (a man and a woman), three before the experimental session (sessions 1, 2 and 3) and the other three (sessions 5, 6 and 7) after the experimental session (session 4). The psychotherapy before the experimental sessions consisted of preparing subjects for the possibility of an MDMA experience, and therapy sessions after the experimental session consisted of discussing the events and material from the experimental session with subjects so that they could understand and integrate the MDMA experience into everyday life. Each nondrug session was 90 minutes long, while the experimental sessions lasted six hours plus another two hours of rest. Blood pressure and heart rate were measured every 30 minutes during the first six hours of the experimental session. At hour 8, all subjects went home accompanied by a relative or by a close friend. One psychotherapy session took place the day following the experimental session; this session was designed to help the subject further explore and integrate the experiences that took place during the experimental session. The rest of the sessions took place with a five to seven day interval. Subjects filled out a Therapeutic Alliance questionnaire after each session, and a questionnaire of subjective effects after the experimental session. They also filled out a questionnaire assessing side effects 24 hours and again five to seven days after the experimental session. Subjects also completed a battery of psychological tests at the beginning and at the end of the treatment, administered by an independent evaluator (a woman) who was blind to the treatment assignment. Follow-ups were planned at one, three, six, nine and 12 months after the treatment though none of the subjects could be reached for all of the follow-ups. Subjects 1, 3, 4 and 5 underwent the first follow-up, subjects 4 and 5 completed the second follow-up, and only subject 4 completed the third follow-up. No one was reached for the final follow-up at month 12.

Psychological Approach

As described above, the psychological approach involved three 90-minute psychotherapeutic sessions before and after an eight-hour experimental session that included six hours of psychotherapy and two hours of rest before leaving the hospital facilities. During the three psychotherapy sessions before the experimental session, the therapists and subjects discussed the nature of the MDMA experience, stressing its potential lasting benefits as well as the difficulties that might appear during the experience. Two therapists worked with each subject to develop specific objectives for the MDMA session, and they discussed the different phases of the MDMA experience and their potential risks and benefits. During these three preliminary sessions, both therapists and the subject worked with any emotions the subject had associated with the traumatic event, seeking to explore how the subject was affected and what types of internal resources she had to confront the event during the experimental session. During these first three psychotherapy sessions, therapists needed to respect the subject's psychological limits, without forcing her to go farther than she could tolerate. The therapists trained the subject in some relaxation techniques, such as breath control respiration, that could be helpful during the MDMA/placebo experience. The main objective of the first three sessions was to develop a

realistic purpose and to gain a deep knowledge about the impact that the traumatic event retained over the emotional and psychological sphere.

The experimental session was intended to offer subjects a deep psychological experience where they could reexperience the traumatic event without being emotionally overwhelmed, and where they would perceive emotional control as internally rather than externally situated. Immediately after the administration of the MDMA (or the placebo), the patient was invited to wait for the first psychological effects while lying in the bed with eyes closed and practicing the relaxation and breath techniques that she learned in the first three sessions. This time was also used to discuss again the different MDMA phases emphasizing the things that can happen during the beginning and the ending of the effects, perhaps the two most critical phases of the experience. When the subject was relaxed, the therapists played CDs that they had previously selected, and invited the subject to wait for the coming of the effects. The therapists remained with the subject throughout the experimental session, supporting her while she confronted the traumatic event. There was little dialogue between the subject and therapists at this time. After approximately two hours, the therapists invited the subject to sit in a chair and share her experience with them. During the remainder of the session, the therapists and subject worked together to go deeper into the experience and to put it into words in order to keep the experience fixed in the subject's consciousness. Relevant narratives regarding the traumatic event and new insights were intensively discussed, trying to enable the subject to experience as much as possible, emphasizing the importance of organizing new thoughts and emotions. After about six hours of therapy, when both subject and therapists agreed that they had reached a conclusion, the main part of the session ended and the subject and therapists shared a meal. After another two hours of resting and when the therapists judged that drug effects had waned and the subject had reached an ordinary state of consciousness, subjects left the hospital's facilities, driven by a friend or significant other.

The integration session occurred one day after the MDMA/placebo experience. During the integration session, the subject and the therapists began addressing the experimental session in a discussion that continued through the next three psychotherapy sessions. During discussions of the MDMA experience that took place in integration sessions, the therapists tried to keep the subject focused on the benefits she achieved during and after the experience as they worked through difficulties. The therapist and subject worked to help the subject experience and integrate the emotions arising in response to recalling and confronting difficult areas of the experimental session. The therapists worked intensively during the integration sessions to assist the subject in finding strategies for confronting future difficulties in experiencing intensively felt emotions, in order to extrapolate the benefits gained into the future and into the subject's everyday life. In sum, our therapeutic approach was quite similar to that developed in the past (Greer & Tolbert 1998) when MDMA was administered legally in psychotherapy, and to the therapeutic approach that is used in other government approved MDMA/PTSD studies (Ruse et al. 2005).

Psychological Assessment

As our main objective in this study was to assess the safety of a single psychotherapy session using one of five ascending doses of MDMA in patients with chronic PTSD, we used a wide range of psychological tests in order to cover all the symptoms associated with PTSD, including comorbid symptoms. The scales employed were as follows:

Sociodemographic interview: The Semi-Structured Interview about Sexual Assault (Echeburúa et al. 1995) collects sociodemographic data about the victims, the situational and descriptive characteristics of the aggression(s) and aggressor(s), the personal characteristics of the victim before the aggression, and the personal consequences resulting from the aggression.

Outcome psychopathological scales: The Severity of Symptoms Scale for Post-traumatic Stress Disorder (SSSPTSD) (Echeburúa et al. 1997) is an Spanish adaptation of the PSS (PTSD Symptom Scale; Foa et al. 1993); it is based on the DSM-IV criteria for PTSD and designed to assess the principal symptoms of PTSD: re-experiencing (RE), avoidance (A), and increased arousal (IA), plus a supplementary scale (SS) that assesses somatic symptoms related to anxiety. This scale has been found to be sensitive to therapeutic changes, and is useful in planning treatment and in research involving sexually-assaulted women with chronic PTSD (Corral et al. 1995a, b; Echeburúa et al. 1995). The scale is composed of 17 items (global scale—GS, range: 0-51), each one scored in a Likert-type scale from 0 to 3: five items for re-experiencing symptoms (range: 0-15), seven items for avoidance symptoms (range: 0-21), five items for increased arousal symptoms (range: 0-15), and 13 items for the supplementary scale (range: 0-39). For a subject to be included in the study, she had to score more than 15 on the global scale, and more than 5, 6, and 4 on the re-experiencing, avoidance and increased arousal subscales, respectively. No restrictive criteria were established for the rest of the outcome scales.

The State-Trait Anxiety Inventory, State Version (STAI-S; Spielberger, Gorsuch & Lushene 1970) is comprised of two separate self-report scales that measure two independent concepts of anxiety, state (S) and trait (T). State anxiety, which is the only one used in this study, is defined as a transitory emotional state or condition of the human organism characterized by subjective feelings of tension and apprehension and by autonomic hyperactivity. It is variable in duration and intensity. The state scale has 20 items on a Likert scale from 0 to 3 (range: 0-69; cut off point: 31). The Spanish version was adapted by Seisdedos (1982).

TABLE 1
Sample Demographic Information (N = 6)

	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5	Subject 6
Current Age	29	31	32	49	38	35
Age at the Time of the Assault	6-14	30	30	6	5	34
Marital Status	Married	Single	Single	Married	Separated	Married
# of Children	3	0	0	3	0	0
Lives with	Husband and daughters	Parents and brothers	Parents and sister	Husband	Alone	Husband
Educational Level	Literate	Grade School	High school	Grade School	College	Grade School
Profession	None	None	University student	Housewife	Teacher	Pharmacist's assistant
Current Occupation	Unemployed	Unemployed	Unemployed	Housewife	Teacher; mental sick leave	Unemployed
Socioeconomic Level	Low-medium	Low-medium	Medium-High	Medium	Medium	Medium
Place of Attack	Father's home	At work	Istanbul hotel while on holidays	Street	Street, aggressor's house	At work
Time of Attack	Not specified	Not specified	At dawn	Not specified	Afternoon	Between 12-15 pm
Type of Coercion	Verbal threat, physical violence, heavy objects, gun	Verbal threat, physical violence	Physical violence	--	Verbal intimidation	Verbal threat
# of Aggressors	1	1	1	1	1	1
# of Victims	2 (she and her mother)	1	1	1	1	1
Relationship with the Aggressor	Daughter	Employee	Acquaintance	Niece	Granddaughter	Employee
Reaction to Aggressor	--	Tried to persuade and resist	Gave in to the threat	Gave in to the threat	Gave in to the threat	Tried to persuade
Acts Committed by the Aggressor	Insults & threat, blows & cuts, body touching, masturbation	Insults & threat, blows & cuts, body touching, masturbation	Anal coitus	Vaginal coitus	Body, touching anal coitus	Vaginal coitus
Was Attack Reported?	No	Yes	No	No	No	No

The Beck Depression Inventory (BDI; Beck et al. 1961) is composed of 21 items, each of which evaluates a symptom of depression. Each item has four possible responses, from 0 to 3 according to the intensity of the symptom (Range: 0-63; cut off point: 18). It assesses depression, giving greatest importance to cognitive symptoms. The Spanish version was adapted by Conde & Franch (1984).

The Hamilton Rating Scale (HAM-D; Hamilton 1960) is focused more on the behavioral and physiological symptoms of depression, which makes it a good complement to the BDI scale. It is composed of 21 items plus one final item to specify other symptoms, which are measured on a scale of either three or five points, depending on the item (range: 0-84; cut off point: 18). The Spanish version of this scale was also adapted by Conde & Franch (1984).

The Modified Fear Scale (MFS III; Veronen & Kilpatrick 1980)is a self-report measure based on the "Fear Questionnaire" (Wolpe & Lange 1964) with the addition of 42 items related to issues specific to sexual assault. In this study, we used the version containing only these additional

TABLE 2
Direct Scores per Subject and Group Mean Values for the Psychopathological Assessment Scales (N = 6)

	Subject 1 MDMA (50 mg)	Subject 2 Placebo	Subject 3 MDMA (50 mg)	Subject 4 MDMA (50 mg)	Subject 5 MDMA (75 mg)	Subject 6 Placebo	Group Mean Placebo (N = 2)	Group Mean MDMA 50 mg (N = 3)
Pre	43 (14; 19; 10; 29); 35; 37; 41; 148; 26; 22	45 (13; 17; 15; 22); 38; 21; 26; 111; 22; 37	32 (8; 15; 9; 11); 51; 24; 51; 95; 30; 21	37 (15; 14; 8; 25); 30; 16; 25; 104; 21; 31	48 (14; 19; 15; 32); 34; 25; 60; 132; 28; 24	44 (12; 13; 13; 28); 19; 19; 45; 128; 18; 18	44.5 (12.5; 15; 13.5; 25); 28.5; 20; 35.5; 119.5; 20; 27.5	37.3 (12.3; 16; 9; 21.6); 38.6; 25.6; 39; 115.6; 25.6; 24.6
Post	25 (10; 10; 5; 18); 24; 28; 32; 127; 24; 20	39 (11; 16; 12; 9); 25; 16; 21; 69; 26; 40	20 (5; 8; 7; 13); 29; 3; 10; 69; 0; 35	40 (15; 17; 8; 29); 24; 14; 24; 115; 20; 27	32 (14; 9; 9; 9); 24; 1; 19; 78; 20; 33	41 (13; 16; 12; 28); 31; 31; 44; 152; 20; 20	40 (12; 16; 12; 18.5); 28; 23.5; 22.5; 110.5; 23; 30	28,3 (10; 11.6; 6.6; 20); 25.6; 15; 22; 103.6; 14.6; 27.3
Follow-up #1 (1 month)	37 (10; 19; 8; 25); 37; 41; 45; 147; 26; 16	--	21 (5; 9; 7; 13); 35; 5; 7; 73; 3; 21	17 (9; 6; 2; 14); 27; 4; 13; 88; 18; 34	31 (5; 9; 16; 10; 21) 28; 21; 39; 96; 22; 22	--	--	25 (8; 8.3; 5.6; 17.3) 33; 16.6; 21.6; 102.6; 15.6; 23.6
Follow-up #2 (3 months)	--	--	--	17 (8; 7; 2; 17); 24; 1; 11; 86; 18; 30	28 (4; 10; 14; 16); 27; 14; 43; 86; 24; 25	--	--	--
Follow-up #3 (6 months)	--	--	--	27 (10; 11; 6; 9); 23; 0; 15; 72; 18; 31	--	--	--	--
Follow-up #4 (9 months)	--	--	--	--	--	--	--	--
Follow-up #5 (12 months)	--	--	--	--	--	--	--	--

Note: The figures appeared in each box correspond in this order to: SSSPTSD (RE; A; IA; SS); STAI/S; BDI; HAM-D; MSF III; MS; SE/R.

items. Responses are made on a Likert-type scale ranging from 1 to 5 (score range: 45-225; no cut off point specified). The Spanish version of this scale was adapted by Echeburúa and collagues (1995).

The Maladjustment Scale (MS; Echeburúa & Corral 1998) is composed of six items, each of which refer to one of the following factors related to social and work-related adjustment: work and/or studies, social life, free time, intimate relationships, family life, and overall life. Responses are made on a Likert-type scale from 1 to 6 (range: 0-30; no cut off point specified).

The Rosenberg Self-Esteem scale (SE/R; Rosenberg 1965) is a self-report measure consisting of 10 items, with responses made on a Likert scale from 1 to 4 (range: 14-40; cut off point: 29) that evaluates elements from self-acceptance to self-esteem expressed in a general sense. The Spanish version was adapted by Maldonado (1988).

Subjective effects scale: The Hallucinogen Rating Scale (HRS; Strassman et al. 1994) consists of 100 items, with individual items assessing one of six factors: somaesthesia (reflecting somatic effects); affect (sensitive to emotional and affective responses); volition (indicating the volunteer's capacity to willfully interact with herself and/or the environment); cognition (describing modifications in thought process or content); perception (measuring visual, auditory, gustatory, and olfactory experiences); and intensity (which reflects the strength of the overall experience). The Spanish version was adapted by Riba and colleagues (2001). The computation range for all the subscales is 0 to 4.

Side effects scale: The UKU Scale of Secondary Effects (Lingjaerde et al. 1987) is a scale that assesses the clinical side effects of the use of psychoactive medications at therapeutic dosages, whether in daily use or in clinical studies. It consists of 43 items that measure four groups of effects: psychological (P), neurological (N), anatomical (A) and others (O). Each symptom is evaluated as being absent (0), mild (1), moderate (2), or severe (3).

Therapeutic alliance scale: The Penn Helping Alliance Questionnaire (HAq; Alexander & Luborsky 1986) is a scale for measuring the patient's experience of the helping alliance. The subject completed the HAq at the end of each session. The HAq consists of 11 items that the subject

TABLE 3
Improvements of Each Subject and Group Between the Pre, Post and Follow Ups (N = 6)

	Subject 1 MDMA (50 mg)	Subject 2 Placebo	Subject 3 MDMA (50 mg)	Subject 4 MDMA (50 mg)	Subject 5 MDMA (75 mg)	Subject 6 Placebo	Group Mean Placebo (N = 2)	Group Mean MDMA 50 mg (N = 3)
Pre-Post	18 (4; 9; 5; 11); 11; 11; 9; 21; 2; -2	6 (2; 1; -3; 13); 13; 5; 5; 42; -4; 3	12 (3; 7; 2; 12); -2; 22; 23; 41; 26; 30; 14	-3 (0; -3; 0; -3); 6; 2; 1; -11; 1; -4	16 (0;10; 6; 23); 10; 24; 41; 54; 8; 9	3 (-1;-3; -1; 0); -12; -12; 1; -24; -2; 2	4.5 (1; -1; 2; 6.5); 0.5; -3.5; 3; 9; -3; 2.5	9 (2.3; 4.3; 2.3; 2); 13; 12; 17; 12; 11; 2.6
Pre-Follow-up #1	6 (4; 0; 2;4); -2; -4; -3; 1; 0; -6 -	--	11(3; 6; 2; 11); 2; 16; 19; 44; 22; 27; 0	20 (6; 8; 6; 11); 3; 12; 12; 16; 3; 3	17 (9;3;5;11); 6; 4; 21; 36; 6; -2	--	--	12.3 (4.3; 4.6; 3.3; 4.3); 5,6; 9; 17.6; 19.5; 10; -3
Pre-Follow-up #2	--	--	--	20 (7; 7; 6; 8); 6; 15; 15; 18; 3; -1	20 (10; 9; 1; 16); 7; 11; 17; 46; 4; 1	--	--	
Pre-Follow-up #3	--	--	--	10 (5; 3; 2; 16); 7; 16; 19; 32; 3; 0	--	--	--	--
Pre-Follow.up #4	--	--	--	--	--	--	--	--
Pre-Follow.up #5	--	--	--	--	--	--	--	--

Note: The figures appeared in each box correspond in this order to: SSSPTSD (RE; A; IA; SS); STAI/S; BDI; HAM-D; MSF III; MS; SE/R.

responds to using a scale ranging from +3 to –3 according to the degree of agreement she feels with each statement (range: +33 to -33). The scale also contains two open-ended questions about ways in which her condition has improved or worsened after treatment, and one question about overall improvement on the Likert-type scale running from 1 to 5. The Spanish version of this questionnaire was adapted by Poch & Ávila (1998).

RESULTS

Demographic Data

The demographic data of the sample, gathered by the use of the semistructured interview, are summarized in Table 1. The ages of the six women ranged from 29 to 49 years old. Regarding educational level, one woman never went to school, three out of the six had finished elementary studies, another had finished secondary school, and the last had finished university studies. Regarding the sexual aggression, two out of six women suffered anal rape, another two vaginal rape and the other two body touching and other kinds of sexual aggression.

Psychological Assessment

Table 2 shows the direct scores obtained by each subject in each outcome psychopathological scale and subscale at the pretreatment stage, at post-treatment, and at follow-ups; Table 3 shows the amount of improvement attained by each subject in these variables and at these same evaluation times. Because only six subjects were treated in this clinical trial, it was not possible to perform any statistical analysis comparing between groups, so the present analysis is only descriptive. Thus, in addition to the direct scores of each subject, the means obtained by each group in each scale and subscale have been calculated. Since most of the subjects only underwent one follow-up assessment, statistical analyses cannot make within-subjects comparisons across time.

MDMA induced higher subjective effects in subject 5 (75 mg) than in the any of the 50 mg group (Table 4), and an improvement in almost all the outcome scales (Tables 2 & 3). In the Severity of Symptoms Scale for Post-traumatic Stress Disorder results we find that at the post-treatment phase subject 5 (75 mg) improved seven points more as compared with the 50 mg group, while the 50 mg group improved 4.5 points as compared to the placebo group, who improved 4.5 points. The total improvement for subject 5 was 16 points between pre- and post-treatment, 17 points between pre-treatment and the first follow up (vs. 12.3 points for the 50 mg group), and 20 points between pre-treatment and the second follow up. By comparison, the total improvement for the placebo group at the post-treatment was 4.5 points,

TABLE 4
Direct Scores per Subject and Mean Values per Group for the Hallucinogen Rating Scale

	Subject 1 MDMA (50 mg)	Subject 2 Placebo	Subject 3 MDMA (50 mg)	Subject 4 MDMA (50 mg)	Subject 5 MDMA (75 mg)	Subject 6 Placebo	Group Mean Placebo (N = 2)	Group Mean MDMA 50 mg (N = 3)
Somaesthesia	1.23	0.00	1.23	0.00	2.54	0.69	0.345	0.82
Affect	1.47	0.00	1.18	0.24	2.06	0.29	0.145	1.17
Perception	0.00	0.06	0.29	0.00	1.88	0.12	0.09	0.723
Cognition	1.33	0.00	1.17	0.50	2.92	0.25	0.125	1.176
Volition	1.00	0.00	1.38	1.00	2.50	0.00	0.00	1.126
Intensity	1.00	0.00	1.75	0.00	2.75	0.00	0.00	0.916

TABLE 5
Direct Scores per Subject Group Mean Values for the Helping Alliance Questionnaire

	Subject 1 MDMA (50 mg)	Subject 2 Placebo	Subject 3 MDMA (50 mg)	Subject 4 MDMA (50 mg)	Subject 5 MDMA (75 mg)	Subject 6 Placebo	Group Mean Placebo (N = 2)	Group Mean MDMA 50 mg (N = 3)
Session 1	14	17	26	10	19	8	12.5	10
Session 2	11	--	24	18	--	13	13 (n=1)	17.6
Session 3	10	27	27	9	30	15	21	15.3
Session 4 (MDMA/ placebo)	18	26	28	18	24	15	20.5	21.3
Session 5	18	27	29	11	25	19	23	19.3
Session 6	18	33	27	16	26	22	27.5	20.3
Session 7	--	33	30	29	31	3	15.2	29.5 (n=2)

and for the 50 mg group 9 points, and 12.3 points between pre-treatment and the first follow-up.

Subject 5 also showed greater improvement than the 50 mg group and the placebo group on the first and second follow-ups in the STAI/S. Subject 5 attained lower scores than the placebo and the 50 mg group subjects on post-treatment and follow-up measures on both depression scales (BDI and HAM-D), and in the MFS III. The 50 mg group scored lower than the placebo group in all PTSD symptoms, and higher on subjective effects. The 50 mg group scored better than subject 5 on the MS, and both 50 mg group subjects and subject 5 scored better than the placebo group. This is because subject 3 (50mg) had a dramatic reduction in her scores, destabilizing the mean value for the 50 mg group. However, comparing subject 5 with subjects 1 and 4, we can see that subject 5 improved more than the other two. In the SE/R, subject 5 attained higher post-treatment scores than the other groups, and though at the first follow-up the 50 mg group scored one point higher than subject 5 as compared to pretreatment, by the second follow-up subject 5 improved one point more when compared to the pretreatment scores.

All subjects except subject 6 had a higher therapeutic alliance, indicated via higher HAq scores post-treatment when compared with pretreatment scores, though the data do not suggest that this improvement is related to undergoing the experimental session (see Table 5).

Side-Effects Assessment

The UKU scale of side effects was administered 24 hours and seven days after the experimental session. Only subjects 1 (50 mg) and 5 (75 mg) reported very mild side effects at the 24 hour assessment (Table 6). As shown in Table 7, neither blood pressure nor heart rate reflected notable increases at any time during the experimental session when compared with baseline values.

Other Assessments

Table 8 shows the doses of MDMA in milligrams per kilogram received by each subject. Table 9 shows time in days between last day of menstrual cycle and experimental session, and Table 10 shows what both subjects and therapists believed concerning the dose administered during the experimental session, including whether it was placebo or MDMA and beliefs concerning dosage.

DISCUSSION

This report is about the world's first fully approved, controlled study to investigate the safety of administering

TABLE 6
Secondary Effects for Subjects 1 (MDMA 50 mg) and 5 (MDMA 75 mg) 24 Hours after the Experimental Session

Symptom	Severity	Causal Relationship	Interference with Patient's Daily Performance Medical Criteria	Interference with Patient Opinion	Consequence
Concentration difficulties (P)	-- ; 2	-- ; 1	-- ; 1	-- ; 2	-- ; 0
Asthenia/Lassitude/ Increased Fatigability (P)	3 ; 3	1 ; 1	0 ; 1	0 ; 3	0 ; 0
Sleepiness/Sedation (P)	3 ; 2	0 ; 1	0 ; 1	0 ; 2	0 ; 0
Failing memory (P)	-- ; 2	-- ; 1	-- ; 1	-- ; 1	-- ; 0
Depression (P)	-- ; 1	-- ; 1	-- ; 1	-- ; 1	-- ; 0
Tension/Inner Unrest (P)	2 ; 1	2 ; 1	0 ; 1	0 ; 2	0 ; 0
Emotional indifference (P)	-- ; 1	-- ; 1	-- ; 0	-- ; 0	-- ; 0
Palpitations/Tachycardia (A)	2 ; --	2 ; --	0 ; --	0 ; --	0 ; --
Diarrhea (A)	-- ; 1	-- ; 0	-- ; 0	-- ; 0	-- ; 0
Photosensitivity (O)	2 ; --	2 ; --	0 ; --	0 ; --	0 ; --
Dismissed sexual desire (O)	1 ; --	1 ; --	0 ; --	0 ; --	0 ; --
Tension headache (O)	3 ; 3	2 ; 2	0 ; 3	0 ; 3	0 ; 0
Migraine headache (O)	-- ; 3	-- ; 2	-- ; 3	-- ; 3	-- ; 0
TOTAL SCORE	**16 ; 19**	**10 ; 11**	**0 ; 12**	**0 ; 17**	**0 ; 0**
RANGES	**0-129**	**0-98**	**0-147**	**0-147**	**0-147**

Note: The first figure in each box belongs to subject 1 and the second to subject 5. Only the symptoms scored by the subjects are listed.

TABLE 7
Systolic/Diastolic Blood Pressure and Heart Rate

	Subject 1 MDMA (50 mg)	Subject 2 Placebo	Subject 3 MDMA (50 mg)	Subject 4 MDMA (50 mg)	Subject 5 MDMA (75 mg)	Subject 6 Placebo	Group Mean Placebo (N = 2)	Group Mean MDMA 50 mg (N = 3)
0 min. (base line)	105/73 69	108/71 72	124/73 72	140/100 87	102/76 80	111/92 91	109.5/81.5 81.5	123/82 76
30 min.	103/72 71	104/89 112	110/85 73	160/110 87	104/81 87	111/89 85	107.5/89 98.5	124.3/89 77
60 min.	115/79 79	108/81 73	111/87 73	140/110 85	112/83 75	105/88 72	106.5/84.5 72.5	122/92 79
90 min.	119/76 85	114/68 98	121/84 71	140/110 96	126/93 83	120/87 64	117/77.5 81	126.6/90 84
120 min.	111/71 73	101/67 69	118/79 76	150/110 96	130/89 71	113/84 71	108.5/75.5 70	126.3/86.6 81.6
150 min.	124/80 76	117/76 72	119/79 72	140/110 100	120/80 71	106/84 71	111.5/80 71.5	127.6/89.6 82.6
180 min.	116/68 75	96/75 81	121/77 83	140/110 120	121/87 80	106/88 71	101/81.5 76	125.6/85 92.6
210 min.	104/66 91	115/71 83	118/78 78	140/110 96	117/82 91	103/80 65	109/75.5 74	120.6/85.3 88.3
240 min.	103/72 73	103/70 87	118/78 85	150/110 101	97/73 80	109/84 66	106/77 76.5	123.6/86.6 86.3
270 min.	105/73 69	115/81 116	121/80 80	150/110 109	108/76 91	103/82 73	109/81.5 94.5	125.3/87.6 86
300 min.	105/73 69	92/67 85	118/83 81	140/110 108	116/88 89	105/82 75	98.5/74.5 80	121/88.6 86
330 min.	103/72 71	101/63 85	108/79 76	120/100 105	122/82 91	108/82 71	104.5/72.5 78	110.3/83.6 84
360 min.	105/73 69	102/62 85	120/83 83	120/100 103	120/80 89	113/84 73	82/73 79	115/85.3 85

TABLE 8
Doses into mg/kg Received per Subject

	Subject 1 MDMA (50 mg)	Subject 2 Placebo	Subject 3 MDMA (50 mg)	Subject 4 MDMA (50 mg)	Subject 5 MDMA (75 mg)	Subject 6 Placebo
Weight	61.3 kg	50 kg	57.9 kg	56 kg	53 kg	56.3 kg
Doses (mg/kg)	0.76	--	0.81	0.83	1.41	--

TABLE 9
Day of the Last Menstruation before the Experimental Session

	Subject 1 MDMA (50 mg)	Subject 2 Placebo	Subject 3 MDMA (50 mg)	Subject 4 MDMA (50 mg)	Subject 5 MDMA (75 mg)	Subject 6 Placebo
Last menstruation	28 days	7 days	14 days	Menopausal	17 days	27 days

TABLE 10
Subject and Therapist's Beliefs Regarding the Administered Dose

	Subject 1 MDMA (50 mg)	Subject 2 Placebo	Subject 3 MDMA (50 mg)	Subject 4 MDMA (50 mg)	Subject 5 MDMA (75 mg)	Subject 6 Placebo
Subject	Low dose	Placebo	Low/medium	Placebo	Medium	Medium
Therapist 1	50 mg	50 mg	50 mg	50 mg	75 mg	75 mg
Therapist 2	placebo	50 mg	50 mg	50 mg	75 mg	75 mg

MDMA to a patient population. Though the clinical trial was originally planned to include 29 women with chronic PTSD who had previously failed to respond to conventional treatments, only six subjects could be treated before political pressure resulted in the sudden termination of the study (Caudevilla 2006; Caudevilla 2003; Bouso 2003; Bouso & Gómez-Jarabo 2003; Doblin 2002). Since then, two other clinical trials assessing the safety and efficacy of MDMA-assisted psychotherapy in patient populations have been approved in the U.S., one of them with PTSD patients in which 16 out of 20 subjects have been treated generating very promising data, and the other one with advanced-stage cancer patients with anxiety arising from their diagnosis and short life expectancy. Ethics boards and regulatory agencies have approved another two clinical trials using MDMA-assisted psychotherapy in subjects with PTSD, one study in Israel and the other in Switzerland (see www.maps.org/mdma for detailed information regarding these studies).

The study reported on in this article followed an ascending-dose, placebo controlled, double-blind design, with subjects in each dose condition randomly assigned to receive MDMA or placebo. An evaluator blind to condition assignment and not present during psychotherapy performed the psychological assessment. Two out of six subjects received placebo, three received 50 mg of MDMA, and one received 75 mg of MDMA. The subjective effects of MDMA were greater in the subject who received 75 mg as compared to subjects who received 50 mg, inasmuch as this subject obtained the greatest reduction in almost all the outcome scales employed, including the PTSD scale. The finding that the 75 mg subject obtained better scores on outcome measures as compared to the 50 mg group, and that the 50 mg group improved more than the placebo group, supports greater efficacy as doses increase, at least within the range studied here. As is true of psychotherapies involving exposure to traumatic memories or trauma-associated items, one of the main risks of MDMA psychotherapy for the treatment of PTSD is that the reexperiencing of the traumatic event could induce retraumatizations. It is interesting to note that none of the subjects in this study showed increased scores in the reexperiencing subscale at the post-treatment phase or at the follow-ups. It is also interesting to note that subject 5 had the highest score on the PTSD scale at the pretreatment phase yet she experienced the greatest improvement of all the subjects. Given these findings, it would be important to explore the effects of higher doses of MDMA in order to see what dose exhibits the best outcomes with the fewest side effects. Based in part on accounts of therapy occurring before the scheduling of MDMA (e.g. Stolaroff 1997; Greer & Tolbert 1986), ongoing and planned studies of MDMA-assisted therapy are administering a 125 mg dose of MDMA, and several studies

will include the possibility of administering a supplemental dose of 62.5 mg. (see www.maps.org/mdma). An ongoing randomized, placebo-controlled comparison of two sessions of MDMA-assisted therapy with 125 mg MDMA for people with PTSD has produced encouraging preliminary findings and no drug-related serious adverse events (Mithoefer 2006, 2004). The study now includes the opportunity for participants assigned to the placebo condition to take part in an open-label study continuation. Recently, the FDA and the institutional review board overseeing the study permitted the addition of a third experimental session and the use of a supplemental dose of 62.5 mg MDMA or placebo, administered 2 to 2 1/2 hours after the initial dose. To date, experimental sessions using supplemental doses have gone without incident. This suggests that doses of at least 125 mg will prove safe and efficacious in this patient population.

As the objective of this study was to assess the safety of MDMA in a chronic PTSD population, a wide range of psychopathological scales was used in order to measure not only PTSD symptoms, but also its associated comorbidities, such as anxiety, depression, phobias, maladjustment and damaged self-esteem. Neither of the two doses of MDMA increased symptomatology in any of the psychopathological scales in any of the subjects treated, thus demonstrating that the doses administered in this trial were psychologically safe for all the subjects. Blood pressure, heart rate and other somatic side effects were also assessed and showed no significant elevation, again suggesting that the doses administered were physiologically safe. Because of the variations along all the measurements, it is not possible to establish a dose-response curve for blood pressure and heart rate in this study. Subject 4 met criteria for tachycardia and for hypertension at some points during the MDMA session but her scores can be considered between the range of safety since previous research has reported elevations in blood pressure and heart rate without any need for medical intervention (Mas et al. 1999; Vollenweider et al. 1998). The doses of MDMA used in this study also were found to be both psychologically and physiologically safe in previous clinical pharmacological trials with nonpatient populations (Ramaekers & Kuypers 2006; Cami et al. 2000; Grob et al. 1996). Lastly, one of the two therapists believed that subject 1 received placebo while she actually received a 50 mg dose of MDMA, and both therapists and the patient believed that subject 6 received a 75 mg dose of MDMA while she actually received placebo; and they believed that subject 2 received a low dose of MDMA while she actually received the placebo. Furthermore, subject 4 believed that she received placebo while she actually received a 50 mg dose, and subject 6 also believed that she received a medium dose of MDMA while she actually received a placebo. All those data suggest that, at least for low doses, the double-blind approach is effective in MDMA/PTSD research.

In conclusion, low doses of MDMA administered as an adjunct to psychotherapy were found to be safe for the six subjects with chronic PTSD treated in this clinical trial and there were promising signs of efficacy and reduced PTSD symptomatology. Further studies with a larger sample size and with the administration of higher doses of MDMA are clearly needed in order to clarify both the safety and the efficacy of MDMA-assisted psychotherapy in patient populations.

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