A randomized, controlled pilot study of MDMA (± 3,4-Methylenedioxymethamphetamine)-assisted psychotherapy for treatment of resistant, chronic Post-Traumatic Stress Disorder (PTSD)

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Abstract: Psychiatrists and psychotherapists in the US (1970s to 1985) and Switzerland (1988-1993) used MDMA legally as a prescription drug, to enhance the effectiveness of psychotherapy. Early reports suggest that it is useful in treating trauma-related disorders. Recently, the first completed pilot study of MDMA-assisted psychotherapy for PTSD yielded encouraging results. Designed to test the safety and efficacy of MDMA-assisted psychotherapy in patients with treatment-resistant PTSD; our randomized, double-blind, active-placebo controlled trial enrolled 12 patients for treatment with either low-dose (25 mg, plus 12.5 mg supplemental dose) or full-dose MDMA (125 mg, plus 62.5 mg supplemental dose). MDMA was administered during three experimental sessions, interspersed with weekly non-drug-based psychotherapy sessions. Outcome measures used were the Clinician-Administered PTSD Scale (CAPS) and the Posttraumatic Diagnostic Scale (PDS). Patients were assessed at baseline, three weeks after the second and third MDMA session (end of treatment), and at the 2-month and 1-year follow-ups. We found that MDMA-assisted psychotherapy can be safely administered in a clinical setting. No drug-related serious adverse events occurred. We did not see statistically significant reductions in CAPS scores ($p = 0.066$), although there was clinically and statistically significant self-reported (PDS) improvement ($p = 0.014$). CAPS scores improved further at the 1-year follow-up. In addition, three MDMA sessions were more effective than two ($p = 0.016$).

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Title:

A randomized, controlled pilot study of MDMA (±3,4-methylenedioxymethamphetamine)-assisted psychotherapy for treatment resistant, chronic posttraumatic stress disorder (PTSD)

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Abstract:

Psychiatrists and psychotherapists in the U.S.A. (1970s-1985) and Switzerland (1988-1993) used MDMA legally to enhance the effectiveness of psychotherapy. Early reports suggest its usefulness in treating trauma-related disorders. Recently, encouraging results from the first completed pilot study of MDMA-assisted psychotherapy for PTSD were published. In this study, designed to test safety and efficacy of MDMA-assisted psychotherapy in patients with treatment-resistant PTSD, 12 patients were enrolled in a randomized, double-blind, active-placebo controlled trial using a low dose (25 mg plus 12.5 mg supplemental dose) and a full dose of MDMA (125 mg plus 62.5 mg supplemental dose). MDMA was administered during 3 experimental sessions interspersed with weekly non-drug psychotherapy sessions. Outcome measures were the Clinician-Administered PTSD Scale (CAPS) and Posttraumatic Diagnostic Scale (PDS). Patients were assessed at baseline, three weeks after the second and third MDMA session (end of treatment), at two month and one year follow-up.

MDMA-assisted psychotherapy can be safely administered in a clinical setting. No drug-related serious adverse events occurred. Statistically significant reductions in CAPS scores were not shown ($p=0.066$), though there was clinically and statistically

significant self-report (PDS) improvement (p=0.014). CAPS scores improved further at one-year follow-up. Three MDMA sessions were more effective than two (p=0.016).

Keywords:

Methylenedioxymethamphetamine, MDMA, MDMA-assisted psychotherapy, psychotherapy, posttraumatic stress disorder, PTSD, entactogen

Introduction:

Posttraumatic stress disorder (PTSD) is a common problem in everyday medical practice and a major and costly public health problem all over the world. Lifetime prevalences in the general population range from below 1 % in European countries (Perkonigg et al. 2000, Hepp et al. 2005) up to an average of 8% in countries such as the USA (Breslau et al. 1991, Kessler et al. 1995) although more recent surveys in the Netherlands and Switzerland now show rising rates of 7.4% in adults, and 4.2% in adolescents respectively (de Vries and Olff 2011, Landolt et al. 2012, submitted). In specific populations (e.g. soldiers returning from military service) prevalence can be much higher (Hoge et al 2004). Psychotherapy has been recognized to be the most effective form of treatment for PTSD (van Etten et al. 1998). First-line treatments are exposure-based

therapies such as Cognitive Behavior Therapy (CBT), Prolonged Exposure (PE), Cognitive Processing Therapy (CPT) or Eye Movement Desensitization and Reprocessing (EMDR) (Cloitre 2009, Benedek et al 2009, Foa et al. 2009). While demonstrating efficacy for some patients, studies of CBT show high drop-out rates (20%) and limited effects on PTSD symptoms with up to 58% of study completers still meeting PTSD diagnosis after treatment and only 32-66% reaching a good level of end-state functioning (Schnyder 2005, Foa 2009). Despite better understanding and growing efficacy of existing psychotherapies, PTSD often remains a chronic illness with high rates of psychiatric and medical comorbidity (Jacobsen et al. 2001, McFarlane 2010) and suicidality (Panagioti et al. 2012). Serotonergic agents such as SSRIs and SNRIs are often used to treat PTSD and comorbid disorders or for patients unable to undergo psychotherapy. The only two FDA-approved drugs for this indication, sertraline and paroxetine (Brady et al. 2000, Tucker et al. 2001), show only modest effects on PTSD symptoms. Recent literature reviews stress the importance of developing more effective medications and psychotherapeutic treatments for chronic PTSD (Foa et al. 2009, Stein et al. 2009).

MDMA (±3,4-Methylenedioxymethamphetamine)-assisted psychotherapy is a novel approach to the treatment of PTSD that employs the psychoactive compound MDMA

as a catalyst of PTSD-specific psychotherapy itself. MDMA is a substituted phenylethylamine first synthesized in 1912 by Merck, rediscovered in the 1970s by the chemist A. Shulgin and introduced to psychotherapy by the psychotherapist L. Zeff (Benzenhoefer and Passie 2006). Prior to the U.S. scheduling of MDMA as a drug of abuse in 1985, reports suggested it to be effective in psychotherapy (Metzner and Abramson 2001, Greer and Tolbert 1986). The first rigorously controlled clinical trials of MDMA-assisted psychotherapy in the treatment of chronic PTSD showed promising results (Bouso et al. 2008, Mithoefer 2011). The benefits of MDMA-assisted psychotherapy appear to be long-lasting (Mithoefer et al. In press).

The current neurocircuitry model of PTSD postulates exaggerated and uncontrolled responses of the amygdala to trauma-specific cues as well as deficient top-down inhibition of the amygdala by the ventromedial prefrontal cortex (vmPFC), orbitofrontal cortex and the hippocampus (Rauch et al 2006, Frewen 2006). MDMA increases activity in the vmPFC and decreases activity of the left amygdala (Gamma et al. 2000) possibly reversing some of the above-mentioned abnormalities associated with PTSD. MDMA leads to a transporter-mediated release of serotonin and activation of the 5HT receptor and to a lesser extent to the release of dopamine and norepinephrine. Many

of the positive subjective effects can be attributed to the release of serotonin (Farre et al. 2007; Liechti et al. 2001), and as has been shown recently also of norepinephrine (Hysek et al. 2011). A main characteristic of the MDMA induced state is a positively toned cognitive-emotional state with reduced fear, possibly facilitating processing of traumatic material and better encoding of positive emotional experience. It is theorized that therapeutic exposure to traumatic memories should be kept in an "optimal arousal zone" avoiding the extremes of overwhelming anxiety and other painful emotions (that may lead to) dissociation on one hand and emotional numbing on the other (Ogden and Pain 2005). MDMA may widen this window enhancing affect tolerance and reducing numbing. The pronounced increases in levels of the neurohormone oxytocin under MDMA (Wolff et al. 2006) have been associated with the prosocial effects of MDMA (Dumont et al. 2009, Bedi 2009). The quality of the therapeutic alliance has been recognized as being crucial for the recovery from PTSD (Charuvastra and Cloitre 2008) and the extensive release of oxytocin under MDMA has been postulated to be a prominent factor in improvement of the therapeutic alliance regularly observed in clinical-therapeutic settings under MDMA (Johansen and Krebs 2009). The main postulated psychological effects relevant to the context of MDMA-assisted psychotherapy are

partially based on clinical impressions and also on clinical data from Vollenweider et al.1998, Johanson and Krebs 2009, Passie and Dürst 2009 as shown in Table 1.

This study was intended to serve as a proof of concept and to secondarily confirm the initial findings of the Mithoefer et al.'s (2010) study with a different therapist team. We examined safety and efficacy in an outpatient setting, that included overnight stays after each MDMA session in the clinic for safety reasons, in a small sample of twelve patients with chronic, treatment-resistant PTSD and providing a one year follow-up. A methodological challenge is the maintenance of the double-blind when using a profoundly psychoactive substance like MDMA, since MDMA's effects can be easily discerned by subjects and investigators. In the Mithoefer et al. study (2011), there were difficulties in maintaining the study blind using an inactive placebo control and it is possible that this difficulty affected study results. This study therefore attempted to address the question of whether the use of 25mg of MDMA as an "active placebo" could optimize blinding. We also hypothesized that three MDMA sessions were more effective than only two, and that reductions in PTSD symptoms would remain stable at the one year follow-up.

Methods:

Recruitment and screening procedure

Subjects were recruited for the study by a call for referrals from psychiatric hospitals, trauma counseling centers, psychiatrists and psychotherapists in the German speaking part of Switzerland. Prospective participants were first screened by a scripted telephone interview to check for inclusion and exclusion criteria. Those who met criteria had an informational meeting with the investigator, which included the administration of the Clinician-Administered PTSD Scale (CAPS) to provide PTSD diagnosis. Written informed consent was then obtained from subjects by the investigators. Medical evaluation included a medical history, standard physical examination, ECG, metabolic profile, measurement of thyroid hormones, serum electrolytes, HIV, urinary drug and pregnancy tests (when appropriate). Subjects aged older than 40 years with a positive family history of coronary heart disease and/or presenting risk factors underwent a stress ECG. Psychiatric evaluation and confirmation of the PTSD diagnosis were conducted by an independent rater using CAPS and Structured Clinical Interview for DSM (SCID) I and II. Enrollment began in September 2006 and ended in October 2009. A twelve-month follow-up was completed in January 2011. This study was approved by the ethics committee of the cantons of Solothurn and Aargau/Switzerland and was

conducted according to the regulatory guidance for protection of human subjects and relevant federal regulations and international standards.

Subjects

Twelve subjects (ten female, two male, mean age = 41.4, SD 11.2 years) meeting all inclusion and exclusion criteria were enrolled and completed the study. Two additional subjects discontinued treatment after the first experimental MDMA session. All subjects who were enrolled met DSM-IV-text revision (TR) criteria for PTSD with treatment-resistant symptoms as indicated by a CAPS score of $\geq$ 50 and having previously undergone at least six months of psychotherapy and three months of treatment with an SSRI. Seven of twelve subjects had experienced one or more evidence based therapies: three subjects CBT, one exposure based therapy not specified, one EMDR, three anxiety management not specified and six subjects had had non-evidence based therapies such as insight-oriented therapies. Many of the subjects had undergone multiple therapies and it was not possible any more to exactly identify in all cases the specific method that had been applied. Subjects were required to taper all psychotropic medication before entering the study. Gabapentin was allowed for pain control. Exclusion criteria included significant medical conditions, except for hypothyroidism under hor-

monal replacement. Exclusionary psychiatric conditions were: history of psychotic illness, bipolar disorder type I, borderline personality disorder, dissociative identity disorder and substance abuse or dependence within 60 days of enrollment. Comorbid anxiety disorders, depression as well as eating disorders without active purging were allowed. Subjects who had taken MDMA on more than five occasions or less than six months prior to enrollment were excluded.

One subject had previously used “ecstasy” on three occasions; one had consumed magic mushrooms (psilocybin) several times, the other subjects were completely naïve to psychedelic drugs. Two subjects (one female, one male) discontinued treatment after the first experimental MDMA session. Eleven of twelve subjects who completed the study also participated in the 12-month follow-up. One female subject did not complete the twelve-month follow up because she died six months after finishing the MDMA-assisted treatment from a brain metastasis arising from relapse of breast cancer; this subject had been in remission from her breast cancer for over ten years and had not been symptomatic at screening.

Index traumata included physical and sexual abuse during childhood in six subjects, sexual assault in one, medical treatment in one, motor vehicle accident in two and life

threatening illness in two subjects. The mean duration of PTSD symptoms at enrollment was 18.3 years (SD ± 12). The mean duration of previous psychotherapeutic treatments was 85.8 months (SD ± 71.4).

Subjects were allowed to continue ongoing psychotherapy with outside/referring therapists, but were not allowed to increase the frequency of ongoing treatments, or commence any new therapy until after the administration of outcome measures at two months after MDMA session #3.

Description of study design

In "Stage 1", eight subjects were randomized in a double-blind manner to the full dose and four to the "active placebo" condition with three doses of MDMA administered in three all day-long MDMA-assisted psychotherapy sessions. Full dose consisted of 125 mg followed 2.5 hours later by 62.5 mg MDMA; the "active placebo" dose consisted of 25 mg followed 2.5 hours later by 12.5 mg MDMA. The 125 mg dose of MDMA was chosen on the basis of case reports of MDMA-assisted psychotherapy (Greer and Tolbert 1986, Widmer 1998) as well as on preliminary data obtained from the Mithoefer 2011 pilot study. The dosages chosen for the low dose condition were selected on the

basis of their ability to produce minimal but detectable subjective effects (Grob et al. unpublished; Harris et al. 2002) and thus serve as an “active placebo”. The cumulative dose of 37.5 mg MDMA was not expected to produce a significant reduction in anxiety or a significant increase in access to emotionally upsetting material, though this dosage may produce slight alterations in perception, increased relaxation or tension (Harris et al. 2002). The study allocated a greater number of participants to the full dose condition (2:1) to better assess the safety of the full dose and to enhance recruitment efforts.

Outcome measures:

Outcome measures included two measures of PTSD symptoms:

The *Clinician-Administered PTSD Scale (CAPS)* is a DSM-IV based structured clinical interview designed to quantify PTSD symptoms that has been determined to have excellent psychometric properties of reliability and validity (Weathers et al, 2001). A validated German version of the CAPS was used (Schnyder et al. 2002), serving as screening and main outcome measure.

The *Posttraumatic Diagnostic Scale (PDS)* (Foa et al. 1993; Foa et al. 1997) is a validated self-report measure assessing presence of PTSD symptoms as described in the DSM-

IV serving as an additional outcome measure. An unvalidated yet widely used German version (Ehlers et al. 1996) was used in this study.

The CAPS and SCID I substance abuse module were administered at baseline (T0), three weeks after MDMA-session #2 (T1); three weeks after MDMA-session #3 (T2; end of treatment); two (T3), six (T4) and twelve (T5) months after MDMA-session #3 (follow-up). The PDS was administered one day after each MDMA session; three weeks after MDMA-session #3 (T2; end of treatment); two, six, and twelve months after MDMA-session #3 (T3, T4, T5; long term follow-up LTFU). All outcome measures were administered by a blinded, independent rater. Subjects were tested for drugs of abuse before MDMA sessions, and one time at random during Stage 1 and 2 and at each follow-up testing. Pregnancy tests were performed in women of childbearing potential before each MDMA session. The blind was broken following assessment by the independent rater after the end of Stage 1 treatment. Subjects assigned to the "active placebo" condition were offered an open label continuation of the study with the fully active dose of MDMA ("Stage 2") with identical psychotherapy and assessment as in "Stage 1". CAPS scores from the three weeks post MDMA #3 testing served as baseline

for “Stage 2”. All subjects in the “active placebo” condition in “Stage 1” proceeded to “Stage 2”. Follow-up assessments consisting of the CAPS and PDS were completed two (T3), six (T4) and twelve (T5) months after the final MDMA-session #3.

After preliminary analysis of data showed insufficient clinical response to the experimental treatment in several full-dose subjects, an amendment to the protocol was obtained allowing for two additional sessions of MDMA-assisted psychotherapy for subjects deemed showing insufficient response, referred to as “Stage 3” and employing a dose of 150 mg MDMA and supplemental dose of 75mg MDMA unless contraindicated for safety reasons. Response was considered clinically insufficient on the basis of the investigator’s and patients’ subjective impression of a lack of significant improvement and CAPS change scores (baseline to 2 months after the third experimental session) ≤ 15 points (Weathers 2001, Schnurr 2007), CAPS item #25 ≥ 3 and overall CAPS score still ≥ 50 points at outcome measurement two months after the third MDMA-session served as additional guidelines for the assessment of clinically insufficient response. All three conditions had to be fulfilled.

MDMA

The MDMA (+/-3,4-methylenedioxymethamphetamine) was obtained from a supply originally synthesized by Lipomed AG/Switzerland. The investigational product (125, 62.5, 25 and 12.5mg) was prepared in gelatin capsules of identical appearance and weight by the Laboratory Dr. Bichsel in Interlaken/Switzerland. Quality control and randomization was performed by R. Brenneisen, Department of Clinical Research, Phytopharmacology, Bioanalytics & Pharmacokinetics, University of Bern, Switzerland.

Psychotherapy

The treatment is described in the manual for MDMA-assisted psychotherapy in patients with PTSD (Mithoefer 2011, published online). Two preparatory sessions aimed at establishing a therapeutic alliance and preparing subjects for the MDMA experience preceded the first MDMA session. The MDMA sessions took place in group psychotherapy room at the first author's clinic. Subjects arrived at nine a.m. After testing for drugs of abuse and females for pregnancy, session goals and intentions were recapitulated. The MDMA was ingested at ten a.m. Subjects were instructed to remain reclining on the mattress, to focus attention inward, keep eyes closed as much as possible and to allow the inner process to unfold. The therapeutic tools used to guide the subjects consisted of:

1. A program of music which was designed to support the subject's experience by aiding relaxation and/or evoking and supporting deep emotions and the emergence of unconscious material (Bonny and Savary 1990, Spitzer 2002).
2. MDMA-assisted psychotherapy is primarily focused on experiencing and is only to a lesser extent a verbal method during the MDMA sessions themselves. Discussions between therapists and participant take place only when needed. The therapeutic approach is generally non-directive, following and encouraging the MDMA-induced psychological process.
3. Focused body work was defined as bodily contact that employs nurturing touch (e.g. hand-holding) and touch aimed at intensifying and thereby releasing body tension and pain by giving resistance for the subject to push against. It is always performed with explicit consent from the subject and respecting individual boundaries and vulnerabilities.

The therapists (one male and one female) were present during the entire session. MDMA-sessions lasted approximately eight hours, after which the subjects were offered a light meal and a previously designated support person (e.g. spouse) arrived to stay with them overnight at the clinic. A non-drug psychotherapy session took place

the morning after each MDMA experience, followed by two sessions one week apart aimed at ensuring the integration of the experiences from the MDMA-sessions. The therapist attitude was supportive, validating the MDMA experience and facilitating understanding and emotional clearing. Following each MDMA session, the subjects were contacted via telephone by one of the therapists on a daily basis for one week in order to assess the subject's psychological well-being and monitor drug after-effects. Subjects received a total of twelve non-drug psychotherapy sessions. Additional sessions in case of excessive distress were limited to two after each MDMA session.

Further Assessment and Safety Measures

Subjects' blood pressure (BP) and heart rate (HR) were measured 15 and five minutes before ingestion of the MDMA, afterwards every half-hour for four hours and then every hour until termination of the session. Body temperature was measured 15 minutes before MDMA administration and hourly until termination of the session. The degree of psychological distress was monitored repeatedly during the course of each MDMA session with a one-item visual analog scale, the Subjective Units of Distress. The participant's beliefs concerning condition assignment were collected during the

non-drug psychotherapy session the day after each MDMA session. The therapists collected any spontaneously reported reactions over a seven-day period starting on the day of each experimental session.

Statistical Analysis

CAPS and PDS scores were analyzed by nonparametric analysis of variance (ANOVA) using an F1-LD-F1 model (Brunner and Langer (1999), Brunner et al. (2002)) with the experimental intervention condition (full dose MDMA versus "active placebo" MDMA) serving as a between-group factor and time of measurement serving as a within-subjects factor. Given an insufficient number of participants in "Stage 2" for formal analysis, scores were compared across the two stages to see whether "Stage 2" scores were reduced compared to "Stage 1" scores. The Wilcoxon Signed-Rank-Test for paired data was used to analyze whether a third MDMA session improved CAPS scores compared to only two MDMA sessions. Group comparisons of vital signs pre- to post-session (excluding data from the high dose group due to insufficient sample size) were performed by first averaging the values for each subject over the three sessions to obtain an "average" day and then calculating a nonparametric 95% confidence interval covering the true median of the differences (pre- to post-session). To compare the

magnitude of the difference between the maximally observed value and the baseline value between treatment groups, a similar approach as above was chosen: To show that the values of the increase are higher on average in the full dose group than in the placebo group, a lower confidence bound B for the difference of increase, such that the true value of increase (full dose) – increase ("active placebo") is as least as big as B with a confidence of 95%, was computed. Given the small sample size no adjustments for covariates were made and the study had only sufficient power to detect large effects. Therefore, there was no adjustment for multiple testing; unadjusted exact p-values and confidence intervals were reported instead. Results were considered significant when $p \leq 0.05$. Trends were also reported when $p \leq 0.1$. The F1-LD-F1 models were computed with SAS 9.1, all other analyses were performed with the statistics program R 2.7.1.

Results:

Efficacy: Figure 1 shows the course of CAPS and PDS scores over time in the two groups. Interestingly, the average CAPS scores in the "active placebo" group increased slightly from T1 to T2. The three interaction relative treatment effects (RTE) T0-T2 for total CAPS scores in the full dose group showed a distinct decrease in CAPS scores with

time compared to the active placebo group in the ANOVA but narrowly missed statistical significance (p=0.066). On average, CAPS scores decreased 15.6 points (23.5%) in full dose subjects. There was a significant simple effect of time in the full dose group (p=0.002), meaning that the time effect was significant only in the full dose group. The simple time effect for the active placebo group was not significant (p=0.475). For the other two models T0 vs. T1 and T1 vs. T2 group and time effects and interaction were not significant. PDS scores decreased in the full dose group compared to an increase in the “active placebo” group. There was a significant interaction effect of group and time (p=0.014).

A Wilcoxon Signed Rank test for paired data was performed to test whether three MDMA sessions were more effective than only two sessions. There was a significant difference in CAPS scores (p=0.016, exact p-value to account for ties) between the two time points T1 and T2.

The median prior psychotherapy treatment times of the „active placebo“and the full dose group were 123 and 39.9 months. A comparison of the two distributions using the two-sample Wilcoxon rank sum test yielded a two-tailed p value of 0.154.

Safety: There were no serious drug-related adverse events and medical intervention was not required during or following MDMA sessions.

Rescue medication: Zolpidem for insomnia was offered for the first nights after MDMA sessions but was administered on only one occasion. Most subjects refused sleep medication, frequently commenting that lying awake was not experienced as being distressing but an opportunity to reflect on the still ongoing inner process. Lorazepam for anxiety/distress related to the processing of the traumatic memories was administered in six out of nine subjects after ten out of 56 full dose or 150 mg MDMA sessions, typically during the week after MDMA sessions, with five of these six subjects having been on antidepressants and/or benzodiazepines at enrollment. In all cases single doses of 1-2mg lorazepam reduced the anxiety or distress adequately. Only one subject with no psychotropic medication at enrollment required lorazepam on one occasion. In the "active placebo" group lorazepam was administered to two of five subjects after three low dose MDMA sessions. Both had been treated with antidepressants and/or benzodiazepines at enrollment. The other three active placebo subjects did not need any medication nor had they had any psychotropic medication at enrollment. Except for the subject who was subsequently diagnosed with a prefrontal brain metastasis and

who experienced a panic attack, the anxiety that required medication was related to the PTSD. Acetaminophen or mefenamic acid (in two subjects with a history of headache refractory to acetaminophen were administered short term for headache following MDMA sessions.

Spontaneously reported reactions: See Table 3. The most commonly reported reactions on the day of the experimental session were moderate insomnia (125mg: 43%, 150mg: 50%), loss of appetite and restlessness in subjects receiving 125mg MDMA, and headache, moderate insomnia (31%) and loss of appetite in subjects receiving 25mg MDMA. Insomnia and loss of appetite were the most commonly reported reactions in both conditions. Restlessness, tight jaw, thirst and feeling cold were commonly reported reactions in the full dose group that were minimally reported in the active placebo group. Dizziness, headache and impaired gait/balance were also frequently reported in both groups. Most reactions resolved when drug effects diminished. Loss of appetite, difficulty concentrating, anxiety, and headache persisted beyond this window to 24 hours, but were self-limiting.

Physiologic data: See Table 4. For both groups temperature values tended to be significantly higher pre- to postsession within the range of between 0.97 and 0.46 degrees

Celsius. In the full dose group, systolic BP and HR did not change significantly (albeit just narrowly which may be due to underpowering). The comparison of the difference between the maximally observed and the baseline value between conditions showed that all lower confidence bounds B were negative meaning the increase in any of the physiological parameters was not significantly higher in the full dose than in the placebo group.

Additional psychotherapy sessions: Additional integrative psychotherapy sessions were conducted as per protocol in situations of excessive distress or other issues following MDMA sessions. Eight out of thirteen subjects who received full dose either in the initial randomization or in the "Stage 2" crossover group required a total 21 additional sessions with no more than four additional sessions per subject and stage (mean 1.6 per subject). In the "active placebo" group (N=5) four additional sessions were provided to the above-mentioned two "active placebo" subjects exhibiting excessive distress (mean 0.8 per subject). One additional session was conducted in "Stage 3" (mean 0.3 per subject)

Clinical Response and LTFU: Clinical response as defined above was observed in four out of eight subjects in the full-dose group with all of them still fulfilling PTSD criteria

but with a reduction in severity from severe to mild (CAPS score 20-39) (n=3) or moderate (CAPS score 40-59) (n=1) PTSD.

Three full-dosage subjects met criteria for being non-responders and were enrolled in "stage 3" with either a full or higher dose of MDMA (two full-dose sessions, two high-dose sessions and two high dose sessions followed by a lower supplemental dose). The dosages were chosen on the basis of clinical judgment. The additional sessions did not lead to any further improvements in CAPS scores (mean CAPS score change 0.3 points). As a result, no further subjects were enrolled in "Stage 3".

In the "active placebo" group all four subjects failed to respond to the treatment with two subjects showing higher CAPS scores and a slight clinical deterioration. In the "Stage 2" crossover group, all four subjects responded to the treatment: two of four subjects no longer fulfilled PTSD criteria and two had improved but still had moderate PTSD. At the one-year follow-up, CAPS scores had decreased by a mean of 24 points (35%) compared to baseline in the full-dose group and 35 points (52%) in the crossover group with nine subjects showing a significant clinical improvement. The majority of subjects continued their previous or another psychotherapy or medication during this time. Also at LTFU, five of twelve subjects no longer met the diagnostic criteria for

PTSD, two had mild PTSD, four had moderate PTSD and one had died of a cause not related to the study. One of four subjects on disability and three fit for limited employment at baseline had returned to work fulltime at the 1-year follow-up.

Blinding: The investigator's guesses on the 14 subjects' condition assignments were correct in eight full dose subjects (including one drop-out) and uncertain in one full dose subject. They were also correct in 2 active placebo subjects, whereas their guesses were incorrect in one and they were uncertain in two active placebo cases (including one drop-out). Thirteen subjects provided guesses concerning condition assignment: The full dose subjects' guesses were correct in four, uncertain in two and incorrect in two cases, with uncertainty defined as changing their condition assignment guess over time. Subjects in the "active placebo" group guessed correctly in two, were uncertain in one case (drop-out) and incorrect in two cases. Combining all the guesses for subjects and clinical investigators and ignoring the level of certainty shows that there were a total of 37 guesses, with 22 (59%) correct and 15 (41%) incorrect. For the 24 guesses of full dose sessions, 16 (66%) were correct and 8 (34%) were incorrect, and for the 13 guesses of low dose sessions, 6 (46%) were correct and 7 (54%) were incorrect. Since there were only two doses in the study producing a 50% chance of a correct

guess by chance alone, the authors conclude that the study blind was successfully maintained based on these results.

Discussion:

This small randomized, blinded pilot study of MDMA-assisted psychotherapy in a population of subjects with chronic, treatment refractory PTSD as encountered in daily psychiatric practice demonstrates that this novel treatment method can be safely applied in an outpatient setting (including an overnight stay for safety reasons after each MDMA session) with no drug-related serious adverse events. Cardiovascular effects and body temperature increases were similar to those reported in the literature and did not require medical intervention. The spontaneously reported reactions occurred in the expected range seen in the literature, and were generally mild and well tolerated. A comparison of the safety profiles between 25 mg and 125 mg did support that the 125 mg dose was associated with more reactions in general. Efficacy failed to reach statistical significance ($p= 0.066$) as measured by the primary outcome measure, the CAPS, whereas self-assessment of the subjects' PTSD symptoms as measured by the self-report questionnaire PDS showed a significant reduction ($p= 0.014$). Three experimental MDMA sessions were significantly more effective than only two ($p= 0.016$).

Further improvement over the one-year follow-up time was unexpected (CAPS score reduction of 35% in “Stage 1” full dose subjects and 52% in “Stage 2” crossover full dose subjects, with nine out of eleven showing clinical response). Since all participants at 12-month follow up had received full-dose MDMA in either “Stage 1” or “Stage 2”, comparisons by condition were not possible at the 12-month follow-up. Four subjects had changed or begun a new therapy during follow-up, two received a SSRI for relapse of depression and one had participated in stage 3. It is therefore unclear to which degree these findings at the 12-month follow-up can be attributed to the experimental treatment.

An unforeseen clinical observation in the “active placebo” group showed that there were two distinct types of reactions to the low dose of MDMA: three of the subjects (including one drop-out) experienced similar but milder psychotherapeutic processes to those of the full dose subjects, including spontaneous recall and reliving of traumatic memories along with intensified negative emotions but without the typical positive and integrative effects of the full dose MDMA-state, suggesting a partial activation of the MDMA-induced state. This state of partial activation (spontaneous recall of trauma but without maximum fear reduction) resembles clinical observations of the early

stages of the MDMA experience in many of the full-dose subjects. Consequently, the resulting (more stressful) form of exposure to the traumatic memories required more support from the therapists during and between MDMA-sessions, was more trying for the subjects, and led to the drop-out of one subject who felt overly stressed by the process. The other two “active placebo” subjects showed no or only slight (pleasant) changes in perception (i.e. being touched by music) and relaxation (i.e. feeling light), which wore off after one hour.

Interestingly, we did not find a placebo response as has been observed in other psychopharmacological studies of PTSD (Davidson 2001, Marshall 2001, Tucker 2001, Mithoefer 2011). This and the observed partial activation of the MDMA state in three of five subjects of the “active placebo” group indicate that psychotherapy with even a low dose of MDMA may influence the course of PTSD and possibly interferes with the placebo effect in some subjects. We postulate that the unfolding of the different aspects of the typical MDMA state in a psychotherapeutic setting (see Table 1) is a function of dose and time.

Additional medication for sleep disorders was needed on only one occasion which is surprising given the fact that many of the subjects experienced chronic insomnia due

to their PTSD and had taken sleep medications in the past and noting that insomnia is a common side effect of MDMA. This result contrasts distinctly to the results of the Mithoefer 2011 study which used an inactive placebo. We interpret this finding as an indication of the enhanced tolerance of distress and aversive emotional states including insomnia under and following MDMA and conclude that sleep medication should be given only on request. Despite this effect on the tolerance of insomnia, the prolonged and intensive exposure to traumatic material inherent to this treatment method can temporarily cause distress and anxiety in the integration phase. The increase in distress may require additional medication with benzodiazepines and/or additional psychotherapy sessions. Benzodiazepines were used as little as possible in order to avoid suppressing the ongoing integration process. It is noteworthy that most of the subjects requiring benzodiazepines after the MDMA intervention had been treated with antidepressants with anxiolytic effects and/or benzodiazepines at enrollment and that only one subject who had been free of anxiolytic or antidepressant medication at enrollment received a benzodiazepine during the study. We postulate that the need for benzodiazepines is more likely to be related to a predisposition for anxiety rather than to direct MDMA effects, therefore is not a safety concern.

It is difficult to interpret the discrepancy between the results of this study and that of Mithoefer and colleagues in terms of the primary outcome (mean CAPS change score 53.7 under MDMA vs. 20.5 points under placebo (p=0.015), clinical response (>30% CAPS score reduction) 83% vs. 25%), given that they followed a similar design, employed the same main outcome measure, administered only two MDMA sessions and noted a distinct placebo effect. We presume that other factors could have influenced outcome such as cultural differences, independent rater differences, therapist differences, or the sample possibly including more cases with a higher degree of overall severity of the illness not captured by the employed screening and diagnostic measures (i.e. personality structure, attachment style, etc.). However, with the small sample size the difference could also have been due to chance.

Limitations: This exploratory study intended to investigate the safety of the method and to serve as proof of concept was underpowered as is acceptable for such phase II studies. Further goals of this study were to test for efficacy and to further develop an optimal research protocol for phase III studies addressing two basic challenges in the investigation of this novel method: the first challenge is that this method is a combination of a psychotherapeutic intervention and a catalyzing psychopharmacological

treatment. To date there are no recognized and standard methods for the investigation of this type of combined therapy and only one rigorously controlled trial has been previously reported (Mithoefer et al 2011). MDMA is not just an augmenting “add-on” medication but rather a catalyst that dramatically influences the psychotherapeutic process itself. This makes it virtually impossible to distinguish pure drug effects from psychotherapeutic effects. The second challenge is that current research standards require the use of double blind RCTs for the assessment of the psychopharmacological part of the method with the difficulty of ensuring an acceptable double-blind. Phase 1 studies investigating MDMA or other psychoactive compounds such as psilocybin have used substances such as methylphenidate, d-amphetamine or nicotinic acid as substances that may mimic some of the effects of the study drug and therefore may be effective as active placebos. Our findings suggest that subjects were successfully blinded to study condition using low dose MDMA as an active placebo and that the blind occurred in both conditions. Clinical investigators were less blinded to subject condition assignment than subjects but the blind was still sufficiently effective in clinical investigators, showing that a small dose of MDMA used as an “active placebo” improved the blinding compared to the study by Mithoefer et al (2011).

Prototypical MDMA effects are expected only at doses over 80mg (Bedi et al. 2009). Three of five active placebo subjects seemed to show partial MDMA effects at much lower doses which enhanced the blind. However the low dose turned out to be less well tolerated psychologically and required more therapist interaction than the fully active dose. A study addressing this question is currently underway (NCT01211405). A further weakness was the lack of power for the statistical analysis for differences of gender and country of origin; most subjects were females and Europeans. It is difficult to generalize from relatively homogenous and small samples. Differences in the duration of previous therapy between "active placebo" and full dose group were not significant ($p=0.083$). In the light of the two drop-outs coming from other cultures (Turkey, South Africa), these possible covariates deserve attention in future studies. The imbalance between the number of "active placebo" and full dose subjects is also a limitation.

Adherence to the manual and inter-rater reliability were tested only post-hoc (data not presented here). The adherence raters viewing session videos from this study and the study by Mithoefer et al (2011) noticed a few areas where our therapy differed some-

what from the manual, in that our approach was considered more directive in some places. Whether this had any impact on outcomes will require additional research.

Conclusions:

From a clinical point of view we recommend that future studies include three instead of only two preparatory sessions to strengthen the therapeutic relationship before administering MDMA. The observed 100% response rate of the crossover subjects in "Stage 2", compared to the 50% response rate of the subjects receiving full dose MDMA in "Stage 1", suggests that strengthening the therapeutic alliance does contribute to enhancing treatment outcomes. Future studies should also find a way to minimize additional psychotherapy sessions, as this could be a potentially confounding factor.

In summary, MDMA-assisted psychotherapy was safely administered, with no drug-related serious adverse events, in a small sample of treatment resistant patients suffering from chronic PTSD. The approach did not, however, produce significant symptom reductions. Further research into MDMA-assisted psychotherapy is warranted to verify the results of the Mithoefer 2011 study.

Conflict of interest:

P. Oehen and V. Widmer received payment from the sponsors for conducting the study and R. Traber received payment as an independent rater. P. Oehen is on the board of directors of the Swiss Medical Association for Psycholytic Therapy, a co-sponsor of the study.

Trial Registration:

Clinicaltrials.gov Identifier: NCT00353938

Previous Presentations:

Interim findings were presented at "The Psychedelic Science in the 21st Century" conference, April 15-18, 2010, San Jose, USA; the "20th IFP World Congress of Psychotherapy" conference, June 16-19, 2010 in Lucerne, Switzerland; the "Mind Altering Science" conference, October 23-24, 2010, Amsterdam, The Netherlands and the "Breaking Convention" conference, April 1-3, Canterbury, UK.

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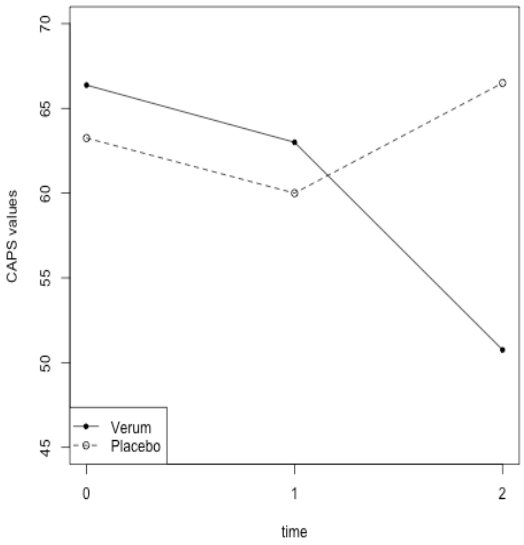
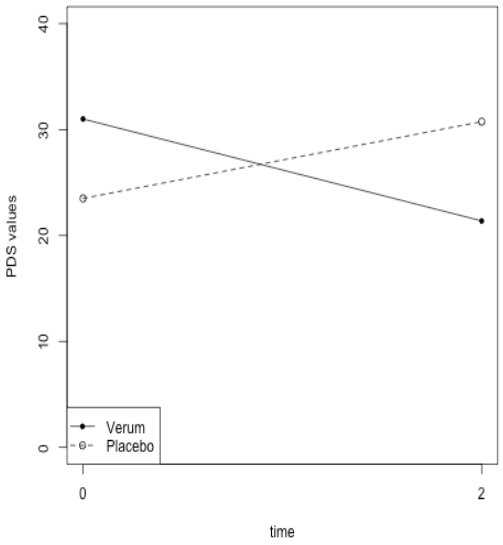
Figure 2:





CAPS mean total scores by group for time TO-T2 (SD)

TO: Baseline < 4 weeks before MDMA and after discontinuation of psychotropic medication
Active Placebo: 63.4 (7.9) Full Dose: 66.4 (13.6)
T1: 3 weeks post MDMA-session 2
Active Placebo: 60.0 (6.8) Full Dose: 63.0 (17.8)
T2: 3 weeks post MDMA-session 3
(end of treatment)
Active Placebo: 66.5 (7.6) Full Dose: 50.8 (19.7)

CAPS Change scores (SD):
T0-T1: Active Placebo: -3.3 (9.9) Full dose: -3.4 (12.0)
T1-T2: Active Placebo: 6.5 (10.3) Full dose: -12.2 (8.1)
T0-T2: Active Placebo: -3.2 (15.3) Full dose: -15.6 (18.1)

PDS mean scores by group for time TO-T2 (SD)

TO: Baseline < 4 weeks before MDMA and after discontinuation of psychotropic medication
Active Placebo: 23.5 (1.9) Full Dose: 30 (6.3)

T2: 3 weeks post MDMA-session 3
(end of treatment)
Active Placebo: 30.8 (6.2) Full Dose: 21.4 (11.9)

Changes scores T0-T2 (SD):
Active Placebo: 7.3 (6.2) Full dose: -8.6 (13.0)

Figure 1:

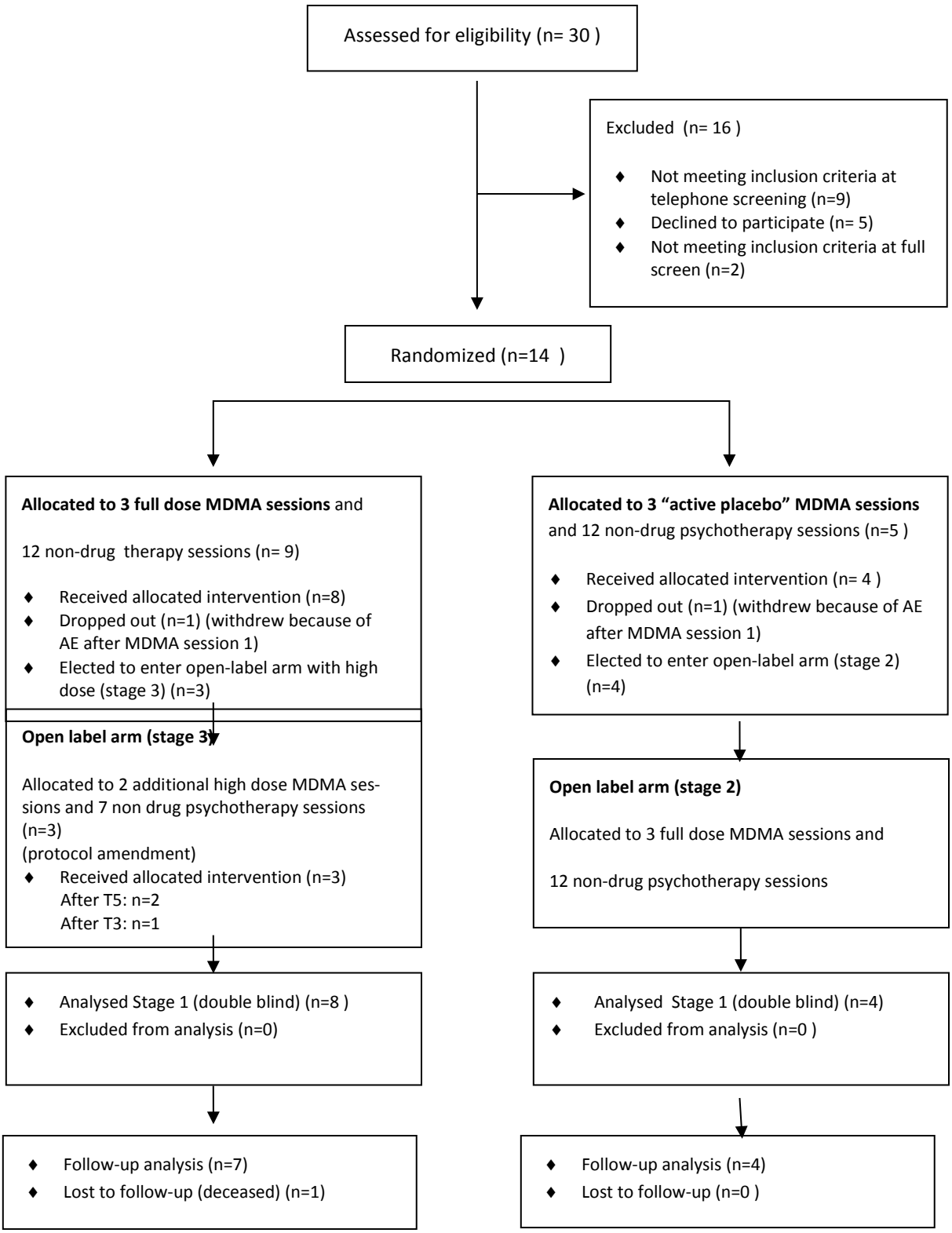

Assessed for eligibility (n= 30)
Excluded (n= 16)
Not meeting inclusion criteria at telephone screening (n=9)
Declined to participate (n= 5)
Not meeting inclusion criteria at full screen (n=2)
Randomized (n=14)
Allocated to 3 full dose MDMA sessions and
12 non-drug therapy sessions (n= 9)
Received allocated intervention (n=8)
Dropped out (n=1) (withdrew because of AE after MDMA session 1)
Elected to enter open-label arm with high dose (stage 3) (n=3)
Allocated to 3 "active placebo" MDMA sessions and 12 non-drug psychotherapy sessions (n=5)
Received allocated intervention (n= 4)
Dropped out (n=1) (withdrew because of AE after MDMA session 1)
Elected to enter open-label arm (stage 2) (n=4)
Open label arm (stage 3)
Allocated to 2 additional high dose MDMA sessions and 7 non drug psychotherapy sessions (n=3)
(protocol amendment)
Received allocated intervention (n=3)
After T5: n=2
After T3: n=1
Open label arm (stage 2)
Allocated to 3 full dose MDMA sessions and
12 non-drug psychotherapy sessions
Analysed Stage 1 (double blind) (n=8)
Excluded from analysis (n=0)
Analysed Stage 1 (double blind) (n=4)
Excluded from analysis (n=0)
Follow-up analysis (n=7)
Lost to follow-up (deceased) (n=1)
Follow-up analysis (n=4)
Lost to follow-up (n=0)

Table 2: Participant characteristics

Characteristic		**Full dose group**	**Placebo group**	**Total**
		n=8	n=4	n=12
Gender	Female	7 (87%)	3 (75%)	10 (83%)
	Male	1 (12%)	1 (25%)	2 (16%)
Mean age (SD)	Range 23 – 67y	42.1 (12.8)	40.0 (6.2)	41.4 (11.2)
Country of origin	Study completers	CH: 7, F: 1	CH: 4	CH: 11, F: 1
	Drop-outs	TR: 1	ZA: 1	
Marital Status	Single	3 (37%)	2 (50%)	5 (41%)
	Married/living with partner	2 (25%)	2 (50%)	5 (41%)
	Divorced/separated	3 (37%)	0 (0%)	4 (33%)
Work status	On disability	4 (50%)	1 (25%)	5 (42%)
	Fit for limited employment	2 (25%)	1 (25%)	3 (25%)
	Working fulltime	1 (13%)	2 (50%)	3 (25%)
	Retired	1 (13%)	0 (0%)	1 (8%)
History of abuse/dependency	Alcohol	1 (13%)	0 (0%)	1 (8%)
	Cannabis	1 (13%)	1 (25%)	2 (17%)
Prior drug use	MDMA (# subjects)	0	1 (3 occasions)	1
	Psilocybin (# subjects)	1	0	1
Mean # years duration of PTSD (SD)	Range 3 - 40y	16.4 (10.9)	22.3 (12.1)	18.3 (12.0)
Mean # months of prior psychotherapy (SD)	Range 22 - 240m	39.9 (73.3)	123 (60.6)	85.8 (71.4)
Comorbid disorder	Unipolar depression	7 (88%)	3 (75%)	10 (83%)
	Panic disorder	0 (0%)	1 (25%)	1 (8%)
	Eating disorder	1 (13%)	0 (0%)	1 (8%)
	Seasonal affective disorder	1 (13%)	1 (25%)	2 (17%)
	Dysthymia	1 (13%)	0 (0%)	1 (8%)
Index trauma	Childhood sexual abuse	4 (50%)	2 (50%)	6 (50%)
	Sexual assault	1 (13%)	0 (0%)	1 (18.%)
	Accident	1 (13%)	1 (25%)	2 (17%)
	Medical treatment	1 (13%)	0 (0%)	1 (28%)
	Life-threatening illness	1 (13%)	1 (25%)	2 (17%)
Medication for PTSD at enrollment		4 (50%)	2 (50%)	2 (50%)

CH: Switzerland; F: France; TR: Turkey; ZA: South Africa

Table 1: Psychological effects of MDMA in the context of psychotherapy

Category	**MDMA-induced state**	**Psychotherapeutic implication**
Mood/Affect	Mild euphoria Anxiety and fear ↓ Enhanced perception of and intensified feelings Affect tolerance↑	Positive and fearless emotional state of well-being Emotional avoidance↓ Tolerance and processing of difficult emotions ("window of tolerance")↑
Cognition/ memory	More imaginative and associative Contemplativeness↑ Recall and tolerance of traumatic memories↑	Recall of relevant traumatic memories↑ Prolonged spontaneous exposure to traumatic memories Cognitive restructuring "simulation of alternative behavior"
Attachment-/ interpersonal Behaviour	Social fears and defensiveness↓ Social approach behaviour↑ with empathy, openness, trust, feelings of being connected to others↑ Cuddling and need for touch↑	Improvement of therapeutic alliance Rebuilding of trusting relationships Defensiveness and isolation↓
Self	Self-esteem ↑ Self-acceptance↑	Grounding/centering↑ Consolidation of self↑
Body	Release of muscular tension Analgesia Sensuality↑	Release of tension and reduction of somatic symptoms Positive body image

Table 4: Spontaneously reported reactions

	Day of MDMA 125 mg Sessions: 37 N (%) (Mean Severity)	**Day of Placebo 25 mg** Sessions: 13 N (%) (Mean Severity)	**Day of MDMA 150 mg** Sessions: 6 N (%) (Mean Severity)	**Within 7 days after 125/150 mg** Sessions: 43 N (%) (Mean Severity)	**Within 7 days after 25 mg** Sessions: 13 N (%) (Mean Severity)
Anxiety	10 (27%) (1.6)	2 (15%) (1.4)	1 (16%) (1.0)	11 (26%) (1.0)	2 (15%) (1.0)
Decreased concentration	6 (16%) (1.1)	0	0	10 (23%) (1.5)	0
Dizziness	8 (22%) (1.0)	4 (31%) (1.0)	3 (50%) (2.3)	8 (18%) (1.6)	3 (23%) (1.3)
Drowsiness	2 (5%) (1.0)	0	0	2 (5%) (1.0)	1 (8%) (1.0)
Dry mouth	7 (19%) (1.1)	0	2 (33%) (1.5)	5 (12%) (1.0)	0
Fatigue	13 (35%) (1.5)	2 (15%) (1.0)	1 (16%) (1.0)	24 (56%) (1.6)	5 (38%) (1.4)
Headache	11 (30%) (1.6)	5 (38%) (1.8)	2 (33%) (1.5)	10 (23%) (1.9)	4 (31%) (1.5)
Heavy legs	1 (3%) (1.0)	0	1 (16%) (1.0)	0	1 (8%) (1.0)
Impaired gait/balance	12 (32%) (1.0)	3 (23%) (1.0)	4 (66%) (1.0)	3 (7%) (1.4)	0
Irritability	0	0	0	9 (21%) (1.3)	1 (8%) (1.0)
Increased private worries	2 (5%) (1.5)	0	0	9 (21%) (1.4)	3 (23%) (1.1)
Insomnia	16 (43%) (2.1)	4 (31%) (1.8)	3 (50%) (2.3)	20 (47%) (1.9)	6 (46%) (1.6)
Jaw clenching	14 (38%) (1.4)	1 (8%) (1.0)	4 (66%) (2.3)	7 (16%) (1.2)	0
Lack of appetite	15 (41%) (1.9)	4 (31%) (2.0)	2 (33%) (2.0)	7 (16%) (1.5)	5 (38%) (1.5)
Low mood	4 (11%) (1.3)	1 (8%) (2.0)	0	20 (47%) (1.4)	6 (46%) (1.4)
Nausea	6 (16%) (1.8)	2 (15% (1.0)	2 (33%) (1.0)	5 (12%) (1.0)	2 (15%) (1.2)
Need for more sleep	1 (3%) (2.0)	0	0	6 (14%) (1.1)	3 (23%) (1.2)
Nystagmus	3 (8%) (1.0)	0	1 (16%) (1.0)	1 (2%) (1.0)	0
Paresthesia	2 (5%) (1.0)	0	1 (16%) (1.0)	0	0
Perspiration	6 (16%) (1.5)	0	2 (33%) (1.0)	1 (2%) (1.0)	0
Restlessness	15 (41%) (1.2)		2 (33%) (1.5)	6 (14%) (1.4)	0
Feeling cold	11 (30%) (1.1)	1 (8% (1.0)	0	6 (14%) (1.2)	1 (8%) (1.0)
Thirst	13 (35%) (1.3)	0	2 (33%) (1.5)	1 (2%) (1.2)	0
Weakness	3 (8%) (1.8)	0	1 (16%) (1.0)	5 (12%) (1.1)	0

N: Number of spontaneous reports (%): N in percentage of sessions Severity: 1 = mild, 2 = moderate, 3 = severe

Table 3: Physiologic Data

MDMA Group		**Full Dose (excl. high dose*)**			**"Active" Placebo (low dose)**		
		Mean/median	(SD)	Range	Mean/median	(SD)	Range
Systolic BP	Baseline	134.3/128.1	(17.3)	106/176.5	121.7/124.3	(5.4)	100/126
	Maximum	160.1/153.7	(21.1)	124/200	139.6/139.3	(10.4)	117/144
	Post	138.8/132.3	(18.4)	111/168	123.3/121.5	(10.6)	107/127
Diastolic BP	Baseline	82.6/80.1	(9.7)	65.8/100.5	77.2/76.3	(2.8)	72/84
	Maximum	95.3/97.4	(11.4)	73/121	88.1/88.5	(7.0)	76/92
	Post	83.3/84.3	(10.9)	65/102	74.4/76.3	(5.5)	68/81
Pulse	Baseline	79.7/80.1	(7.4)	62/109	78.4/79.5	(7.8)	60/94
	Maximum	98.5/105.2	(13.3)	71/121	79.9/100.5	(17.0)	69/124
	Post	85.3/88.7	(11.7)	65/108	81.8/85.1	(11.4)	61/90
Temperature	Baseline	36.6/36.6	(0.33)	35.8/37.6	36.5/36.5	(0.26)	36.3/37.1
	Maximum	37.5/37.5	(0.39)	36.7/38.6	37.6/37.6	(0.4)	36.5/38.5
	Post	37.1/37.3	(0.28)	36.6/37.9	37.2/37.0	(0.4)	36.6/38.0

* Sample size too small for statistical analysis; all values for BP, HR and T were within ranges of the full dose group