MDMA assisted psychotherapy found to have a large effect for chronic post-traumatic stress disorder

Henri Chabrol and Peter Oehen

J Psychopharmacol 2013 27: 865
DOI: 10.1177/0269881113495119

Psychopharm

Journal of Psychopharmacology
27(9) 865–866

DOI: 10.1177/0269881113495119
jop.sagepub.com
SAGE

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Oehen et al. (2013) reported a well-designed, randomized, double-blind, active placebo controlled trial of MDMA assisted psychotherapy in a small sample (*N*=12) of participants with resistant, chronic post-traumatic stress disorder (PTSD). They did not find a statistically significant reduction in clinician-observed PTSD symptoms, although self-reported PTSD symptoms significantly improved. They concluded that 'the approach did not produce significant symptoms reductions'. However, this conclusion is based on improper reliance on statistical analyses inappropriately used on such a small sample. Given that the sample is small, the statistical power of the study using analysis of variance is low (the probability of detecting an effect that is actually present by finding a statistically significant result is low) (Cohen, 1992). A potential solution is to express the findings in terms of effect sizes using Cohen's *d*, which is a way of estimating the magnitude of the difference between two means that is independent of the sample size. When there are two groups in a study, *d* equals the difference between means, divided by the common (pooled) standard deviation. In that case, a *d* value of 0.20 is considered to be a small effect, 0.50 a medium effect and 0.80 a large effect (Cohen, 1992). At three weeks post-treatment, mean (SD) intensity of clinician-observed PTSD symptoms was 66.5 (7.6) (95% confidence interval for the mean: 59–74) in the control group and 50.8 (19.7) (95% confidence interval for the mean: 36–65) in the treatment group whereas the mean (SD) intensity of self-reported PTSD symptoms was 30.8 (6.2) (95% confidence interval for the mean: 25–37) in the control group and 21.4 (11.9) (95% confidence interval for the mean: 12.5–30) in the treatment group. The pooled estimates of the common SD based on the average SD from the two means are 13.6 for clinician-observed PTSD symptoms and 9 for self-reported PTSD symptoms. Thus, *d* is (66.5 – 50.8)/13.6 = 1.15 for clinician-observed PTSD symptoms, and *d* is (30.8 – 21.4)/9 = 1.04 for self-reported PTSD symptoms, indicating a large effect. Thus, given than the full dose group had higher baseline levels of both clinician-observed and self-reported PTSD symptoms than the active placebo group, we can say that these subjects with resistant, chronic PTSD showed, on average, a substantial improvement in PTSD symptoms over the course of MDMA assisted psychotherapy.

University of Toulouse, Toulouse, France

Corresponding author:
H Chabrol, Université de Toulouse, 5 allées Antonio Machado, Toulouse, 31058, France.
Email: chabrol@univ-tlse2.fr

Reply to the Letter to the Editor by H Chabrol

We would like to thank Dr Chabrol for his thoughtful considerations. We are aware that we interpreted the results conservatively, first because this was primarily a pilot study of feasibility and safety, and second because we realized the sample was small and the study underpowered for efficacy.

In detail: the magnitude and the statistical significance of an effect must not be confused. The sample size of our pilot study is small and although the F1-LD-F1 models, especially using the ANOVA type p values (Brunner et al. 2002), are well suited to analyse small samples – as are the exact tests we utilized – we cannot control the probability of a type II error. Accordingly, and as usual in this situation, we may only conclude that no significant effect could be found, and not that there is no difference between groups. In the present situation, the solution to low power is not to be found in better statistical methods, but in increasing the sample size.

As to effect size, we agree with Dr Chabrol's suggestion that this could be of help to interpret the results further. But, due to the small sample size (*N*=12) and the large confidence intervals, the effect size of this single pilot study is only an estimate and of low confidence. We therefore hesitated to include an estimate of the effect size. We decided, after much debate, to not present effect sizes so as to not overstate the study results in the paper.

This study is part of an international series of Phase 2 pilot studies of MDMA-assisted psychotherapy for subjects with chronic, treatment-resistant PTSD. The results of the first completed study were published by Mithoefer et al. (2011). In 2013, three other pilot studies are currently recruiting patients (NCT01211405, NCT01793610 and NCT01689740), and one more is being initiated. Comparing effect sizes across these studies, which all differ to a certain extent in variables of design, will heighten certainty that the effect size of a single study is a true effect. The effect size estimates of our study of 1.0 and 1.4 at long-term follow up (LTFU; 12 months after final MDMA session) were comparable to the Mithoefer et al. 2011

Private practice of Psychiatry and Psychotherapy, Biberist, Switzerland

Corresponding author:
Peter Oehen, MD
Ulmenweg 24a, 4562 Biberist, Switzerland.
Email: peter.oehen@hin.ch

and 2013 studies of 1.2 and 2.2 at LTFU (17–74 months after final MDMA session) in a similar sample of subjects with chronic, treatment-resistant PTSD, but subject to variations in treatment method and cultural context.

The estimated effect sizes found in our study may be used in a meta-analysis of the effects of MDMA-assisted psychotherapy. The study sponsor is planning to utilize effect size estimates from several small Phase 2 studies to evaluate data in preparation for the design of two large Phase 3 multi-site studies.

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