Phase II MDMA Trials

Following the review of MDMA-assisted psychotherapy by the Food & Drug Administration, the scientific journal *Psychopharmacology* retracted three related papers[1-3]. Very briefly, the reasons given by the journal were that severe protocol violations occurred during data collection, which the researchers were aware of but did not disclose, and those data were still included in final analysis. Furthermore, the journal alleges that the authors did not fully declare their competing interests. Two of these studies were pooled analyses of several phase II trials that were included in our report on MDMA[2,3]. As these papers are no longer part of the scientific literature, our analysis of them needs to be removed from the report. In their place, the following section discussing data from four separate phase II trials on the safety and efficacy of MDMA-assisted psychotherapy will be included.

All four of these phase II trials were double-blind, randomized controlled trials with an open-label crossover component[4-7]. Between the studies 86 participants with chronic, treatment-resistant PTSD (including military personnel and first responders[4]) were enrolled. During the primary experimental period, all participants received one to two non-drug preparatory sessions and two to three all-day MDMA-assisted psychotherapy sessions with a team of therapists. Each treatment session included an overnight stay and three to four non-drug integrative sessions, spaced approximately a week apart. Doses of MDMA ranged from 0-125 mg; 0 mg was a true placebo, while 25 mg, 30 mg, and 40 mg were typically considered active control doses, and 75 mg, 100 mg, and 125 mg were considered full experimental doses. Each study also offered participants optional half-doses of the drug approximately two hours after the first dose. Following the primary endpoint, ranging from three weeks to two months after the last experimental treatment session, each study offered participants additional, optional, open-label MDMA-assisted psychotherapy sessions (with the accompanying follow-up integration sessions). The primary outcome for each study was the change in the Clinician-Administered PTSD Scale (CAPS). Secondary outcomes included other measures of PTSD symptoms, depression, sleep quality, perceived growth, personality factors, dissociation, and psychological function. **Each of these studies found that the experimental doses of MDMA, along with psychotherapy, significantly improved CAPS scores as compared with placebo/active control groups**. Furthermore, more of those who received the experimental doses exhibited a clinical response (a >30% reduction in CAPS total severity score from baseline) than did those who received the placebo or active control doses. Additionally, secondary outcomes also generally showed greater improvement in response to higher doses of MDMA as compared with placebo/active control.

References

1. Feduccia, A. A., Jerome, L., Mithoefer, M. C., & Holland, J. (2024). Retraction Note: Discontinuation of medications classified as reuptake inhibitors affects treatment response of MDMA-assisted psychotherapy. Psychopharmacology, 1-1.
2. Jerome, L., Feduccia, A. A., Wang, J. B., Hamilton, S., Klosinski, B., Emerson, A., ... & Doblin, R. (2024). Retraction Note: Long-term follow-up outcomes of MDMA-assisted psychotherapy for treatment of PTSD: a longitudinal pooled analysis of six phase 2 trials. Psychopharmacology, 1-1.
3. Mithoefer, M. C., Feduccia, A. A., Jerome, L., Mithoefer, A., Wagner, M., Walsh, Z., ... & Doblin, R. (2024). Retraction Note: MDMA-assisted psychotherapy for treatment of PTSD: study design and rationale for phase 3 trials based on pooled analysis of six phase 2 randomized controlled trials. Psychopharmacology, 1-1.
4. Mithoefer, M. C., Wagner, M. T., Mithoefer, A. T., Jerome, L., & Doblin, R. (2011). The safety and efficacy of±3, 4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study. Journal of psychopharmacology, 25(4), 439-452.
5. Mithoefer, M. C., Mithoefer, A. T., Feduccia, A. A., Jerome, L., Wagner, M., Wymer, J., ... & Doblin, R. (2018). 3, 4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in

military veterans, firefighters, and police officers: a randomised, double-blind, dose-response, phase 2 clinical trial. The Lancet Psychiatry, 5(6), 486-497.

6. Oehen, P., Traber, R., Widmer, V., & Schnyder, U. (2013). A randomized, controlled pilot study of MDMA (±3, 4-Methylenedioxymethamphetamine)-assisted psychotherapy for treatment of resistant, chronic Post-Traumatic Stress Disorder (PTSD). Journal of psychopharmacology, 27(1), 40-52
7. Ot'alora G, M., Grigsby, J., Poulter, B., Van Derveer III, J. W., Giron, S. G., Jerome, L., ... & Doblin, R. (2018). 3, 4-Methylenedioxymethamphetamine-assisted psychotherapy for treatment of chronic posttraumatic stress disorder: a randomized phase 2 controlled trial. Journal of Psychopharmacology, 32(12), 1295-1307.