A review of 3,4-methylenedioxymethamphetamine (mdma)-assisted psychotherapy

Health & Medicine

The Early Therapeutic Use of MDMA

In the late 1960's, after lysergic acid diethylamide (LSD) was banned, some psychedelic therapists began exploring other drugs as tools to enhance psychotherapy. One, Leo Zeff, was initially introduced to MDMA in 1976 by psychedelic chemist, Alexander “ Sasha” Shulgin, who had been studying psychedelics since the early 1960s (1). Zeff went on to successfully and safely give MDMA, then legal, to many thousands of patients (2). Shulgin, alongside chemist David E. Nichols, published the first report into the effects and pharmacology of MDMA in humans (3).

Not a “ classic” psychedelic drug, but an “ entactogen” (4), MDMA produces a more gentle and easily tolerated state compared to LSD. It is shorter-acting, which makes it more clinically manageable, it enhances feelings of empathy and bonding and allows users to access and process memories of emotional trauma (5).

Psychotherapists using MDMA in the early 1980s, when was called “ Adam” or “ Empathy,” wished to keep it within the clinical research community. But MDMA became rebranded as the more marketable “ Ecstasy” and its non-clinical use spread—especially in the club scene or in large parties called raves. In 1984, in response to rising police seizures of the drug, the DEA announced that it intended to ban the compound. The clinical MDMA research community requested a hearing to debate the DEA's intention, but in May 1985 MDMA was initially placed in an emergency Schedule One category and subsequently became permanently scheduled thereafter, where it has stayed ever since—hugely restricting opportunities for its

research (6). Due to this *Catch 22* situation, very little clinical research was able to take place. This prompted the formation of the US-based research organization, *The Multidisciplinary Association for Psychedelic Studies* (MAPS), which today is spearheading global clinical research of MDMA.

In the mid-eighties, a series of uncontrolled case studies, conducted before the ban, were published. These described the effective use of MDMA with individuals, couples and groups (7 , 8). In 1988 the *Swiss Medical Society for Psycholytic Therapy* conducted individual and group psychotherapy with MDMA and LSD. Over a 100 patients with a wide range of psychiatric problems received an average of eight therapeutic sessions. Over 90% of patients described improvements at 19-months follow-up (9). But in 1993 the Swiss Ministry of Health withdrew permission to continue prescribing MDMA and LSD from the Swiss psychiatrists in the wake of concerns about the lack of research methodology and secondary to an ibogaine-related death of a patient (10). The compassionate use of MDMA has restarted in Switzerland in the last years and currently a few patients are treated each year based on individual authorizations by the Federal Office of Public Health.

Throughout the 1990s, tensions developed between the clinical MDMA community, who proposed MDMA was safe in controlled circumstances, and the media and politicians who favored strict prohibition to control recreational use. During this decade the UK brewing industry sponsored widely publicized anti-Ecstasy campaigns in response to their business being eroded by Ecstasy use (11). Undeterred by the political challenges, MDMA

clinical research continued, with a MAPS-sponsored clinical study gaining approval in 2000 to look at MDMA for PTSD in Spain. But after just 1 year, a political backlash by the Spanish government shut down the study.

Contemporary Clinical Research With MDMA

The first controlled clinical study demonstrating MDMA-assisted psychotherapy was eventually published in 2010—with impressive results (12). Twenty patients with treatment-resistant PTSD received, during a course of non-drug psychotherapy, either inactive placebo or two or three sessions of MDMA (initial dose of 125 mg, followed 2 h later by a further booster of 62. 5 mg). At two and 12-month follow-up, 83% of the experimental group no longer met the criteria for PTSD, compared with just 25% of the patients in the placebo group. There were no drug-related serious adverse events and no adverse neurocognitive effects (12). Long-term follow-up of the cohort of successfully-treated patients demonstrated that remission from PTSD was maintained for up to 6 years (17 to 74 months, mean of 45 months), without having any further doses of MDMA (13).

A second, smaller MAPS-sponsored study in 2013 again explored the potential for MDMA Psychotherapy for treatment-resistant PTSD and showed substantial improvements (14). This study by Oehen was smaller than Mithoefer's and although there was a definite trend in the direction of MDMA therapy being superior to placebo, at first sight the statistics failed to demonstrate a significant reduction in CAPS for the experimental subjects (14). However, a further review of the data, using effect size as a measure, concluded that Oehen had been overly conservative and the results were

indicative of MDMA psychotherapy providing substantial improvements for treatment-resistant PTSD (15).

Further teams in the USA, Israel and Canada then began conducting Phase 2 MDMA trials for PTSD. In 2018 a team based in Boulder, Colorado, USA submitted their results of a dose response model from multiple therapy teams on 28 participants (16). Two active doses (100 and 125 mg) were compared with a low dose (40 mg) session, and later the low dose group crossed over for three open-label active dose sessions. The active groups had the largest reduction in CAPS scores at the primary endpoint. The results at the primary endpoint were not significant, but at the 12 month follow-up the difference from baseline did reach significance. There were no drug-related serious adverse events and the treatment was well-tolerated. A further study demonstrated successful treatment of veterans and first responders with treatment-resistant PTSD (17). All of the contemporary MDMA-assisted psychotherapy studies to date have only been carried out on relatively small numbers of patients. Despite the consistently positive results and good tolerability of the treatments described in these studies above, larger, multisite trials are necessary to demonstrate the level of clinical efficacy and safety required to see MDMA become a licensed medicine. This phase of clinical MDMA research is now underway.

In collaboration with the Food and Drugs Administration (FDA) in America and the European Medicines Agency (EMA) in Europe, the pooled data from all of the MAPS-sponsored Phase 2 trials formed the basis for expansion into multi-site Phase 3 trials of MDMA therapy for PTSD, with FDA-granting

Breakthrough Therapy designation. Study centers for the MAPS phase 3 programme in the USA are now underway. The European sites—in the UK, Netherlands, Germany and the Czech Republic—are in the process of seeking approvals and are projected to start later in 2019, putting MDMA on course to becoming a licensed treatment in 2021 (18).

The Safety of Clinical MDMA

In the early 2000s—at the height of Ecstasy's demonization in the media—a debate around safety dominated the scientific and popular literature. But comparing clinical MDMA use with recreational ecstasy carries no scientific validity. Clinical subjects are screened, monitored throughout, are given pure drug and are closely followed-up for months afterwards. In contrast recreational ecstasy use frequently involves impure samples of MDMA, taking multiple other drugs and often paying little attention to the physiological aspects of the drug experience. Nevertheless, even when one *does* look at recreational ecstasy, which is used by around 750, 000 people every weekend in the UK (19), the rates of morbidity and mortality are low. One study demonstrated that after removing confounding factors of concomitant drugs, there were only three deaths per year attributed solely to MDMA (20). Further studies that control for confounding factors show no evidence of neurotoxicity with MDMA when used in isolation (21) and no lasting neurocognitive impairments (22). Given that Ecstasy has such widespread use—second only to cannabis in popularity as an illicit drug—these epidemiological and experimental data demonstrate its relative safety.

Despite the absence of evidence for chronic adverse effects from clinical MDMA therapy, acutely the MDMA experience may be associated with transient neurocognitive effects, including verbal and spatial memory deficits, slow processing speeds and executive functioning impairments (23). But these resolve after the acute subjective psychological effects of the drug have worn off (24). Over 1, 600 doses of clinical MDMA have being administered in research settings in recent years, with only one report of a drug-related self-limiting serious adverse event and no deaths (18). A large analysis on 166 subjects given MDMA in a controlled setting by Vizeli et al. (25), demonstrated no serious adverse events and showed that MDMA " produced predominantly acute positive subjective drug effects." The analysis also showed that subjective negative drug effects and other adverse effects were significantly more common in women. The paper concluded that, " MDMA administration was overall safe in physically and psychiatrically healthy subjects and in a medical setting."

Compared to other stimulants (particularly cocaine, amphetamine and methamphetamine) addiction to MDMA is very rare. And in the last 15 years of clinical studies with medical MDMA, illicit use of ecstasy after having used it clinically is seldom observed (13).

Clinical MDMA administration typically causes increased blood pressure and heart rate, increased body temperature (25 – 27), jaw tightness, bruxism, reduced appetite, poor concentration, and impaired balance (12). More serious adverse effects have not been observed in the last 15 years of monitored sessions with clinical MDMA (28). Similarly, the low mood,

irritability and fatigue described by Ecstasy users (and dubbed the “ mid-week blues”) is rarely observed in the clinical setting (13 , 29), though low mood has also been reported in healthy subjects after administration of MDMA in controlled settings (30 – 32). Studies suggest these “ blues” are related to recreational users missing sleep, dancing excessively, using other drugs (including alcohol), and going without food (33 , 34)—none of which occur in a clinical setting.

Mechanism of Action of Clinical MDMA

Multiple receptors, neurotransmitters and intermediary processes probably account for MDMA's effects. MDMA mainly acts as a releaser of serotonin (5-HT) and noradrenaline, and to a lesser extent also of dopamine (35 , 36). Typical effects of MDMA can be predominantly attributed to the activation of the 5-HT system (31 , 37 , 38).

Activity at 5-HT $_{1A}$ and 5-HT $_{1B}$ receptors attenuates feelings of depression and anxiety, reduces the amygdala fear response and increases levels of self-confidence (39). Increased feelings of closeness, greater compassion and increased empathy for oneself and others further contribute to positive mood (40 , 41). Increased dopamine and noradrenaline raise levels of arousal and awareness (42 , 43), motivating engagement in therapy and promoting fear extinction (44).

MDMA's effects at alpha-2 receptors, which contribute to the drug's effects on thermoregulation (45), may also contribute a paradoxical relaxation/sedation effect (46), which could be beneficial in the context of trauma-induced hypervigilance. While adrenergic alpha-1 receptors are

involved in the thermogenic response to MDMA in humans (41), alpha-2 receptors do not appear to be critically involved in the psychological effects of MDMA in humans (47).

MDMA has been shown to facilitate the release of oxytocin, the hormone associated with early infantile bonding, which may increase levels of empathy and closeness (48 – 52) and dampen fear-related amygdala activity, causing a decrease in stress response and social anxiety (53 , 54).

Animal studies have demonstrated MDMA increases fear extinction through a mechanism dependent on elevated levels of brain derived neurotropic factor (BDNF) in the amygdala (55 , 56), which might account for the observed phenomenon of MDMA psychotherapy allowing for patients' safe recall of painful emotional memories, that are usually avoided due to the overwhelming negative affect that usually accompanies recall of such events. Increased prosocial feelings (57), improved tolerance for unpleasant memories (58) and enhanced empathy and self-compassion (59), can promote a strong therapeutic alliance to effectively process traumatic memories.

In summary, the combined pharmacological effects of MDMA and the associated subjective psychological experience provide a unique selective impairment of the fear response whilst leaving the other faculties intact. Therefore, MDMA could be “ the perfect drug for trauma-related psychotherapy” (60).

How We Carry Out Mdma-Assisted Psychotherapy

Psychotherapy with MDMA borrows much of its methodology from the earliest research with LSD in the 1950s. The concept of set and setting is central to the totality of the user's experience; where set refers to the user's mindset and setting refers to the environment in which the drug is taken. Much effort goes into developing the optimum psycho-environmental conditions for a clinical MDMA-assisted session (61). A comprehensive study with a 125 mg MDMA dose taken by 166 subjects in a clinical environment, showed 64% of the subjects gave reports that the they found the controlled setting reassuring and it made them feel safe (25).

Therapeutic sessions with MDMA are typically delivered by a male-female co-therapist dyadic pair. However, a recently completed study of MDMA-assisted Psychotherapy combined with Cognitive Behavioral Combined Therapy for couples in which one person had PTSD, used some co-therapy teams with two female therapists (https://clinicaltrials. gov/ct2/ show/NCT02876172). The drug-assisted sessions are non-directive; encouraging the patient to go with the experience. The medicine seems to catalyze the patient's innate healing ability, which does the work (7 , 62). The therapists create a sense of safety and communicate trust in their patient's ability to explore their issues. Eyeshades are frequently employed in MDMA-assisted sessions and the use of music played through headphones is commonplace. Physiological observations such as regular measurements of blood pressure and temperature are also commonplace throughout the MDMA experience.

As well as the MDMA-assisted sessions, the non-drug therapeutic sessions that make up a total course of MDMA psychotherapy are essential for preparation before taking the drug and subsequent integration of the emergent material after the drug sessions. Taken on its own, without adequate pre-drug preparation or post-drug support, MDMA is less likely to have a positive beneficial effect [Mithoefer M—Personal Communication: ‘ Our observation in Phase 2 clinical trials is that the preparation and follow-up visits are often crucial because the nature of this therapeutic process is that symptoms can increase afterMDMAassisted sessions (as they can in any deep processing of trauma), and without proper support this could lead to deterioration and risk of suicide for a subset of people. With proper support these challenges are ultimately useful and part of the healing trajectory rather than an adverse outcome' (2018)]. In training MDMA Therapists for the future, MAPS are currently leading the way with their manualised approach for MDMA-assisted psychotherapy for PTSD.

Future Directions: Broadening MDMA Beyond PTSD

Up till now most MDMA therapy research has been conducted with patients with PTSD. But many people suffering with other chronic mental disorders will describe some degree of pre-morbid trauma, often secondary to sexual or physical child abuse, or more commonly emotional abuse and neglect, which are no less damaging to a person's subsequent development (63). Given that such child maltreatment is particularly prevalent in cases of adult addictions (64), we are now exploring the potential role for MDMA therapy in cases of adult alcohol use disorder.

Alcohol use disorder represents a serious clinical, social and personal burden on its sufferers and a significant financial strain on society. Current treatments, both psychological and pharmacological, are poor, with high rates of relapse after medical detoxification and dedicated treatment programs. The earliest historical roots of psychedelic drug-assisted psychotherapy in the 1950s for alcoholism were associated with LSD-assisted psychotherapy (65). Indeed, Bill Wilson, the founder of *Alcoholics Anonymous* , testified to the powerful potential of psychedelic-assisted therapies for treating alcoholism (66). And contemporary pilot studies with psilocybin therapy for alcohol addiction (67) and psilocybin therapy for nicotine addiction (68) have demonstrated positive results. But MDMA-assisted psychotherapy has never been explored as a treatment for any form of substance use disorder. However, MDMA could be well suited to allow a patient using alcohol as a form of self-medication against a history of childhood trauma to explore and address painful memories without being overwhelmed by negative affect. Furthermore, the acute psychological effects of MDMA, which are typically less perceptually disturbing than those produced by classic psychedelics, may be more easily tolerated by some people. Given that compliance is a critical part of addiction therapy, there are good grounds for exploring MDMA therapy for alcoholism (69). However, it must be borne in mind that the cardiovascular tolerability of MDMA is lower compared with hallucinogens (25 , 50), which prompts the requirement for more robust vital signs monitoring during MDMA therapy compared to classic psychedelic drug-assisted psychotherapy.

The capacity for MDMA to increase feelings of empathy and compassion for the self and others may contribute to improved self-awareness and subsequently reduce the denial of alcohol misuse (70). Similarly, MDMA has been shown to increase feelings of mindfulness, which has been increasingly explored as a potential approach for treating alcohol use disorder (71). This is the hypothesis behind the UK's first ever clinical MDMA Therapy study, the Bristol-Imperial MDMA-for-Alcoholism (BIMA) study (69). The BIMA study enrols participants into an 8-week course of supportive psychotherapy employing elements of Motivational Interviewing. As with all psychedelic-drug assisted psychotherapy courses, most of therapeutic sessions are face-to-face *non* -drug-assisted sessions. Only on two occasions participants are administered open-label sessions of MDMA-assisted therapy. On each drug-assisted session participants receive an initial dose of 125 mg MDMA, followed 2 h later by a “ booster dose” of 62. 5 mg to prolong the experience. Throughout the drug-assisted session, vital signs, including blood pressure and body temperature, are monitored. Participants remain in the treatment center overnight after taking MDMA. Mood, sleep and suicide risk are monitored daily for a week. Participants are followed-up for 9-months post-detox, and outcome measures include safety and tolerability data, quality of life measures, physical and mental health status and drinking behaviors (69). This study will be completed by the end of 2019.

Another area of contemporary research with MDMA therapy has explored the potential for relief of social anxiety associated with autism, in a MAPS-sponsored randomized, double-blind, placebo-controlled pilot study completed at Harbor-UCLA Medical Center and Stanford University (72).

One of the cardinal features of autism is a tendency for a sufferer to lack empathy. It is a recognized anecdotal observation that autistic adults often report reduced empathy-impairments during, and for some time after, taking MDMA (72).

Other contemporary areas of research with MDMA therapy include the potential for MDMA-assisted psychotherapy in treating mood disorders (73) and, relatedly, as an alternative to electro-convulsive therapy (74).

Summary and Conclusion

As MAPS pushes ahead with Phase 3 studies in the USA and Europe for MDMA therapy for PTSD, we are seeing a broadening of the clinical possibilities for the compound. Meanwhile psychiatrists are increasingly recognizing the role played by early psychological trauma in a range of mental disorders beyond that of PTSD (69).

Due to its association with recreational Ecstasy, MDMA has a long-standing label of controversy in the UK. But this narrative must be tackled; partly because the compound is demonstrably safe and efficacious in the clinical setting and partly because politics and erroneous media-driven opinion must not be allowed to dictate the progress of medical research (75). Like everything else, MDMA is not 100% safe. As with all medical interventions—from sticking plasters to cancer chemotherapy—MDMA may be simultaneously both invasive and beneficial and therefore the same principles of evidence-based clinical governance must be applied to psychedelics as they are to other therapeutic approaches (76). Clinical MDMA and recreational ecstasy are incomparable in terms of drug purity,

administration and the screening and monitoring of selected participants. “ Prohibition of MDMA and other illicit drugs increases, not reduces, the potential harms of recreational drug use (75), adds unnecessary costs that put research beyond the financial capabilities of many academic institutions, and therefore hold back progress (77).”

There remains much work to be done to convince critics that a compound that is experienced recreationally by so many people may also, in its clinical form, have benefits for patients suffering with treatment-resistant mental disorders. Meanwhile, psychedelic culture is enjoying a palpable renaissance in both medicine and the media. Against this backdrop, psychiatry and society continue to be burdened with far-from-perfect treatment outcomes for many mental disorders. In this context, given the clinical burden, the lack of treatment efficacy and their continued distress, perhaps the only question we should be asking is: Can we afford *not* to explore MDMA therapy for our worthy patients?

Author Contributions

BS wrote the main body of the paper, including citations. LH and DN added further commentary and reviewed and edited the paper.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgments

The authors wish to thank our other team members of the BIMA study, including Research Associates Dr. Claire Durant and Dr. Sue Wilson, Research Assistant Mr. Steve O'Brien, Night Sitter Lead Dr. Chloe Sakal, and expert service user Kevin Speller. We are grateful to The Alexander Mosley Foundation for their funding support and the Multidisciplinary Association for Psychedelic Studies (MAPS) for academic support with the ongoing study. We are grateful to the local substance misuse service, Addaction, and to Tim Williams for his support locally. And we are thankful to the Bristol University CRIC Centre for hosting the study and to Imperial College London for their academic sponsorship.

References

1. Shulgin A. 3-methoxy-4, 5-methylenedioxy amphetamine, a new psychotomimetic agent. *Nature.* (1964) 201: 1120–1. doi: 10. 1038/2011120a0

2. Stolaroff M. The secret chief revealed: conversations with a pioneer of the underground therapy movement. *Sarasota: Multidisciplinary Association for Psychedelic Studies* (2004).

3. Shulgin AT, Nichols DE. *Characterization of Three New Psychotomimetcs* . In: Stillman RC, Willette RE, editors *. The Psychopharmacology of Hallucinogens.* New York, NY: Pergamon Press (1978).

4. Nichols DE. Differences between the mechanism of action of MDMA, MBDB, and the classic hallucinogens. Identification of a new therapeutic

class: entactogens. *J Psychoactive Drugs.* (1986) 18: 305–13. doi: 10. 1080/02791072. 1986. 10472362

5. Sessa B. Could MDMA be useful in the treatment of PTSD? *Prog Neurol Psychiatry* . (2012) 15: 4–7. doi: 10. 1002/pnp. 216

6. Nutt DJ, King LA, Nichols DE. Effects of Schedule I drug laws on neuroscience research and treatment innovation. *Nat Rev Neurosci* . (2013) 14: 577–85. doi: 10. 1038/nrn3530

7. Greer GR, Tolbert R. A method of conducting therapeutic sessions with MDMA. *J Psychoactive Drugs.* (1998) 30: 371–9. doi: 10. 1080/02791072. 1998. 10399713

8. Greer G, Tolbert R. Subjective reports of the effects of MDMA in a clinical setting. *J Psychoactive Drugs* . (1986) 18: 319–27. doi: 10. 1080/02791072. 1986. 10472364

9. Gasser P. Psycholytic Therapy with MDMA and LSD in Switzerland. *Newslett Multidiscipl Assoc Psychedelic Stud.* (1995) 5: 3–7.

10. Doblin R. *Thesis.* (2000). Available online at: http://www. maps. org/research-archive/dissertation/dissertation. pdf

11. Carey J. *Recreational Drug Wars: Alcohol Versus Ecstasy* . ‘ Ecstasy Reconsidered’ by Nicholas Saunders (1997).

12. Mithoefer MC, Wagner TM, Mithoefer AT, Jerome L, Doblin R. 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. *J Psychopharmacol* . (2010) 25: 439–52. doi: 10. 1177/0269881110378371

13. Mithoefer MC, Wagner MT, Mithoefer AT, Jerome L, Martin SF, Yazar-Klosinski B, et al. Durability of improvement in post-traumatic stress disorder symptoms and absence of harmful effects or drug dependence after 3, 4-methylenedioxymethamphetamine-assisted psychotherapy: a prospective long-term follow- up study. *J Psychopharmacol.* (2013) 27: 28–39. doi: 10. 1177/0269881112456611

14. Oehen P, Traber R, Widmer V, Schnyder U. A randomized, controlled pilot study of MDMA (±3, 4-methylenedioxymethamphetamine)-assisted psychotherapy for treatment of resistant, chronic post-traumatic stress disorder (PTSD). *J Psychopharmacol.* (2013) 27: 40–52. doi: 10. 1177/0269881112464827

15. Chabrol H, Oehen P. MDMA assisted psychotherapy found to have a large effect for chronic post-traumatic stress disorder. *J Psychopharmacol.* (2013) 27: 865–6. doi: 10. 1177/0269881113495119

16. Ota'lora G, Grigsby J, Poulter B, Van Derveer JW III, Giron SG, Jerome L, et al. MDMA-assisted psychotherapy for treatment of chronic posttraumatic stress disorder: a randomized controlled trial. *J Psychopharmacol* . (2018) 32: 1295–307. doi: 10. 1177/0269881118806297

17. Mithoefer MC, Mithoefer AT, Feduccia AA, Jerome L, Wagner M, Wymer J, et al. 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. *Lancet Psychiatry.* (2018) 5: 486–97. doi: 10. 1016/S2215-0366(18)30135-4

18. MAPS. *MDMA Investigational Brochure* . (2017). Available online at: http://www. maps. org/research/mdma/mdma-research-timeline/104-other-mdma-resources/5400-mdma-investigator-s-brochure-and-fda-annual-reportandItemid= 485

19. Sessa B. The ecstatic history of MDMA: from raving highs to saving lives. In: *Breaking Convention Book of Proceedings from the 2013 Conference* . London: Strange Attractor Press. (2015). p. 87 -94.

20. Schifano F, Oyefeso A, Webb L, Pollard M, Corkery J, Ghodse AH. Review of deaths related to taking ecstasy, England and Wales, 1997–2000. *BMJ.* (2003) 326: 80–1. doi: 10. 1136/bmj. 326. 7380. 80

21. Halpern JH, Pope HG, Sherwood AR, Barry S, Hudson JI, Todd D, et al. Residual neuropsychological effects of illicit 3, 4-methelenedioxymethamphetamine (MDMA) in individuals with minimal exposure to other drugs. *Drug Alcohol Dependency.* (2004) 75: 135–47. doi: 10. 1016/j. drugalcdep. 2004. 02. 008

22. Ludewig S, Ludewig K, Hasler F, Vollenweider FX. No lasting effects of moderate doses of MDMA (Ecstasy) on memory performance and mood states in healthy humans. *Biol Psychiatry.* (2003) 53(Suppl): 205S.

23. Hanson KL, Luciana M. *Neurocognitive* function in users of MDMA: the importance of clinically significant patterns of use. *Psychol Med* . (2004) 34: 229–46. doi: 10. 1017/S0033291703001132

24. Kuypers KP, Ramaekers JG. Acute dose of MDMA (75 mg) impairs spatial memory for location but leaves contextual processing of visuospatial information unaffected. *Psychopharmacology.* (2007) 189: 557–63. doi: 10. 1007/s00213-006-0321-7

25. Vizeli P, Liechti ME. Safety pharmacology of acute MDMA administration in healthy subjects. *J Psychopharmacol.* (2017) 31: 576–88. doi: 10. 1177/0269881117691569

26. Mas M, Farre M, de la Torre R, Roset PN, Ortuño J, Segura J, et al. Cardiovascular and neuroendocrine effects and pharmacokinetics of 3, 4-methylenedioxymethamphetamine in humans. *J Pharmacol Exp Ther.* (1999) 290: 136–45.

27. Harris DS, Baggott M, Mendelson JH, Mendelson JE, Jones RT. Subjective and hormonal effects of 3, 4- methylenedioxymethamphetamine (MDMA) in humans. *Psychopharmacology.* (2002) 162: 396–405. doi: 10. 1007/s00213-002-1131-1

28. Doblin R, Greer G, Holland J, Jerome L, Mithoefer MC, Sessa B. A reconsideration and response to Parrott AC (2013). Human psychobiology of MDMA or ‘ Ecstasy’: an overview of 25 years of empirical research. *Hum Psychopharmacol.* (2014) 29: 105–8. doi: 10. 1002/hup. 2389

29. Jerome I. *Personal Communication.* (2017).

30. Vollenweider FX, Gamma A, Liechti ME, Huber T. Psychological and cardiovascular effects and short-term sequelae of MDMA (“ ecstasy”) in MDMA-naive healthy volunteers. *Neuropsychopharmacology.* (1998) 19: 241–51. doi: 10. 1038/sj. npp. 1395197

31. Liechti ME, Baumann C, Gamma A, Vollenweider FX. Acute psychological effects of 3, 4-methylenedioxymethamphetamine (MDMA, “ Ecstasy”) are attenuated by the serotonin uptake inhibitor citalopram. *Neuropsychopharmacology.* (2000) 22: 513–21. doi: 10. 1016/S0893-133X(99)00148-7

32. Liechti ME, Gamma A, Vollenweider FX. Gender differences in the subjective effects of MDMA. *Psychopharmacology.* (2001) 154: 161–8. doi: 10. 1007/s002130000648

33. Curran HV, Travill RA. Mood and cognitive effects of ±3, 4–methylenedioxymethamphetamine (MDMA, ‘ ecstasy’): week-end ‘ high’ followed by mid-week low. *Addiction.* (1997) 92: 821–31.

34. Pirona A, Morgan MJ. An investigation of the subacute effects of ecstasy on neuropsychological performance, sleep and mood in regular ecstasy users. *J Psychopharmacol* . (2010) 24: 175–85. doi: 10. 1177/0269881109102780

35. Verrico CD, Miller GM, Madras BK. MDMA (ecstasy) and human dopamine, norepinephrine, and serotonin transporters: implications for MDMA-induced

neurotoxicity and treatment. *Psychopharmacology.* (2007) 189: 489–503. doi: 10. 1007/s00213-005-0174-5

36. Simmler L, Buser T, Donzelli M, Schramm Y, Dieu LH, Huwyler J, et al. Pharmacological characterization of designer cathinones *in vitro. Br J Pharmacol* . (2013) 168: 458–70. doi: 10. 1111/j. 1476-5381. 2012. 02145. x

37. Bershad AK, Miller MA, Baggott MJ, de Wit H. The effects of MDMA on socio-emotional processing: does MDMA differ from other stimulants? *J Psychopharmacol.* (2016) 30: 1248–58. doi: 10. 1177/0269881116663120

38. Dolder PC, Muller F, Schmid Y, Borgwardt SJ, Liechti ME. Direct comparison of the acute subjective, emotional, autonomic, and endocrine effects of MDMA, methylphenidate, and modafinil in healthy subjects. *Psychopharmacology.* (2018) 235: 467–79. doi: 10. 1007/s00213-017-4650-5

39. Graeff FG, Guimaraes FS, De Andrade TG, Deakin JF. Role of 5-HT in stress, anxiety, and depression. *Pharmacol Biochem Behav.* (1996) 54: 129–41. doi: 10. 1016/0091-3057(95)02135-3

40. van Wel JHP, Kuypers KPC, Theunissen EL, Bosker WM, Bakker K, Ramaekers JG. Effects of acute MDMA intoxication on mood and impulsivity: role of the 5-HT(2) and 5-HT(1) receptors. *PLoS ONE.* (2012) 7: e40187. doi: 10. 1371/journal. pone. 0040187

41. Hysek CM, Fink AE, Simmler LD, Donzelli M, Grouzmann E, Liechti ME. Alpha-adrenergic receptors contribute to the acute effects of MDMA in

humans. *J Clin Psychopharmacol.* (2013) 33: 658–66. doi: 10. 1097/JCP. 0b013e3182979d32

42. Hysek CM, Simmler LD, Ineichen M, Grouzmann E, Hoener MC, Brenneisen R, et al. The norepinephrine transporter inhibitor reboxetine reduces stimulant effects of MDMA (“ ecstasy”) in humans. *Clin Pharmacol Ther.* (2011) 90: 246–55. doi: 10. 1038/clpt. 2011. 78

43. Rothman RB, Baumann MH, Dersch CM. Amphetamine-type central nervous system stimulants release norepinephrine more potently than they release dopamine and serotonin. *Synap N Y* . (2001) 39: 32–41. doi: 10. 1002/1098-2396(20010101)39: 1 <32:: AID-SYN5> 3. 0. CO; 2-3

44. Quirk GJ, Mueller D. Noradrenergic signaling in infralimbic cortex increases cell excitability and strengthens memory for fear extinction. *J Neurosci.* (2008) 28: 369–75. doi: 10. 1523/JNEUROSCI. 3248-07. 2008

45. Bexis S, Docherty JR. Role of alpha2A-adrenoceptors in the effects of MDMA on body temperature in the mouse. *Br J Pharmacol.* (2005) 146: 1–6. doi: 10. 1038/sj. bjp. 0706320

46. Giovannitti JA, Thoms SM, Crawford JJ. Alpha-2 adrenergic receptor agonists: a review of current clinical applications. *Anesthesia Prog.* (2015) 62: 31–8. doi: 10. 2344/0003-3006-62. 1. 31

47. Hysek CM, Brugger R, Simmler LD, Bruggisser M, Donzelli M, Grouzmann E, et al. Effects of the alpha2-adrenergic agonist clonidine on the pharmacodynamics and pharmacokinetics of 3, 4-

methylenedioxymethamphetamine in healthy volunteers. *J Pharmacol Exp Ther.* (2012) 340: 286–94. doi: 10. 1124/jpet. 111. 188425

48. Kirkpatrick MG, Francis SM, Lee R, de Wit H, Jacob S. Plasma oxytocin concentrations following MDMA or intranasal oxytocin in humans. *Psychoneuroendocrinology.* (2014) 46: 23–31. doi: 10. 1016/j. psyneuen. 2014. 04. 006

49. Kuypers KPC, Dolder PC, Ramaekers JG, Liechti ME. Multifaceted empathy of healthy volunteers after single doses of MDMA: a pooled sample of placebo-controlled studies. *J Psychopharmacol.* (2017) 31: 589–98. doi: 10. 1177/0269881117699617

50. Schmid Y, Enzler F, Gasser P, Grouzmann E, Preller KH, Vollenweider FX, et al. Acute effects of lysergic acid diethylamide in healthy subjects. *Biol Psychiatry.* (2015) 78: 544–53. doi: 10. 1016/j. biopsych. 2014. 11. 015

51. Hysek CM, Schmid Y, Simmler LD, Domes G, Heinrichs M, Eisenegger C, et al. MDMA enhances emotional empathy and prosocial behavior. *Soc Cogn Affect Neurosci.* (2013) 9: 1645–52. doi: 10. 1093/scan/nst161

52. Thompson MR, Callaghan PD, Hunt GE, Cornish JL, McGregor IS. A role for oxytocin and 5-HT(1A) receptors in the prosocial effects of 3, 4 methylenedioxymethamphetamine (" ecstasy"). *Neuroscience.* (2007) 146: 509–14. doi: 10. 1016/j. neuroscience. 2007. 02. 032

53. Kirsch P, Esslinger C, Chen Q. Oxytocin modulates neural circuitry for social cognition and fear in humans. *J Neurosci.* (2005) 25: 11489–93. doi: 10. 1523/JNEUROSCI. 3984-05. 2005

54. Domes G, Heinrichs M, Michel A, Berger C, Herpertz SC. Oxytocin improves “ mind-reading” in humans. *Biol Psychiatry* . (2007) 61: 731–3. doi: 10. 1016/j. biopsych. 2006. 07. 015

55. Young MB, Andero R, Ressler KJ. 3, 4-Methylenedioxymethamphetamine facilitates fear extinction learning. *Transl Psychiatry.* (2015) 5: e634. doi: 10. 1038/tp. 2015. 138

56. Young MB, Norrholm SD, Khoury LM, Jovanovic T, Rauch SAM, Reiff CM, et al. Inhibition of serotonin transporters disrupts the enhancement of fear memory extinction by 3, 4- methylenedioxymethamphetamine (MDMA). *Psychopharmacology* . (2017) 234: 2883–95. doi: 10. 1007/s00213-017-4684-8

57. Kamilar-Britt P, Bedi G. The prosocial effects of 3, 4-methylenedioxymethamphetamine (MDMA): Controlled studies in humans and laboratory animals. *Neurosci Biobehav Rev.* (2015) 57: 433–46. doi: 10. 1016/j. neubiorev. 2015. 08. 016

58. Carhart-Harris RL, Wall MB, Erritzoe D, Kaelen M, Ferguson B, De Meer I, et al. The effect of MDMA on recollecting autobiographical memories: an fMRI study with implications for MDMA-assisted psychotherapy. *Int J Neuropsychopharmacol* . (2013) 17: 527–40. doi: 10. 1017/S1461145713001405

59. Kamboj SK, Kilford EJ, Minchin S, Moss A, Lawn W, Das RK, et al. Recreational 3, 4-methylenedioxy-N- methylamphetamine (MDMA) or ‘ ecstasy’ and self-focused compassion: preliminary steps in the development of a therapeutic psychopharmacology of contemplative practices. *J Psychopharmacol.* (2015) 29: 961–70. doi: 10. 1177/0269881115587143

60. Sessa B. MDMA and PTSD treatment: PTSD: from novel pathophysiology to innovative therapeutics. *Neurosci Lett.* (2016) 2016: S0304-3940(16)30490-6.

61. Carhart-Harris RL, Roseman L, Haijen E, Erritzoe D, Watts R, Branchi I, et al. Psychedelics and the essential importance of context. *Psychopharmacol* . (2018) 1: 269881118754710. doi: 10. 1177/0269881118754710

62. Mithoefer M. *A Manual for MDMA-Assisted Psychotherapy in the Treatment of Posttraumatic Stress Disorder; Version 8* . (2016). Available online at: http://www. maps. org/research/mdma/mdma-research-timeline/4887-a-manual-~for-mdma-assisted-psychotherapy-in-the-treatment-of-ptsd

63. Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. *Am J Prev Med.* (1998) 14: 245–58. doi: 10. 1016/S0749-3797(98)00017-8

64. Stewart S H. Alcohol abuse in individuals exposed to trauma: a critical review. *Psychol Bull.* (1996) 120: 83–112. doi: 10. 1037/0033-2909. 120. 1. 83

65. Krebs TS, Johansen PO. Lysergic acid diethylamide (LSD) for alcoholism: a meta-analysis of randomized controlled trials. *J Psychopharmacol.* (2012) 9: 2012. doi: 10. 1177/0269881112439253

66. Haritigan F. *Bill W. Chapter 25 p. 177-179. p. 190-197 and pages 170-171.* New York, NY: St. Martins Press (2000).

67. Bogenschutz MP, Forcehimes AA, Pommy JA, Wilcox CE, Barbosa PC, Strassman RJ. Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study. *J Psychopharmacol* . (2015) 29: 289–99. doi: 10. 1177/0269881114565144

68. Johnson MW, Garcia-Romeu A, Cosimano MP, Griffiths RR. Pilot study of the 5-HT2AR agonist psilocybin in the treatment of tobacco addiction. *J Psychopharmacol.* (2014) 28: 983–92. doi: 10. 1177/0269881114548296

69. Sessa B. Why MDMA therapy for alcohol use disorder and why now? *Neuropharmacology.* (2017) 2017: 4. doi: 10. 1016/j. neuropharm. 2017. 11. 004

70. Jerome L, Schuster S, Berra Yazar-Klosinski B. Can MDMA play a role in the treatment of substance abuse? *Curr Drug Abuse Rev.* (2013) 2013: 6. doi: 10. 2174/18744737112059990005

71. Hsu SH, Grow J, Marlatt GA. Mindfulness and addiction. In: Galanter M, Kaskutas LA, editors. *Recent Developments in Alcoholism* . Vol. 18 (2008). p. 229–50.

72. Danforth AL, Grob CS, Struble C. Reduction in social anxiety after MDMA-assisted psychotherapy with autistic adults: a randomized, double-blind, placebo-controlled pilot study. *Psychopharmacology.* (2018) 2018: 9. doi: 10. 1007/s00213-018-5010-9

73. Riedlinger J, Montagne M. Using MDMA in the treatment of depression. In: Holland J, editor. *Ecstasy: The Complete Guide: A Comprehensive Review of the Risks and Benefits of MDMA* . Rochester, VT: Inner Traditions (2001). p. 261–73.

74. Patel R, Titheradge D. MDMA for the treatment of mood disorder: all talk no substance? *Ther Adv Psychopharmacol.* (2015) 5: 179–88. doi: 10. 1177/2045125315583786

75. Sessa B, Nutt DJ. MDMA, politics and medical research: have we thrown the baby out with the bathwater? *J Psychopharmacol.* (2007) 21: 787–91. doi: 10. 1177/0269881107084738

76. Sessa B. The 21st century psychedelic renaissance: heroic steps forward on the back of an elephant. *Psychopharmacology.* (2017) 2017: 7. doi: 10. 1007/s00213-017-4713-7

77. Sessa B, Nutt DJ. Making a medicine out of MDMA. *Br J Psychiatry* . (2015) 206: 4–6. doi: 10. 1192/bjp. bp. 114. 152751