MIND FOUNDATION

A history of ecstasy science

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> “One of the inescapable facts of life is that with MDMA, as with everything that combines both promise and threat, there are intense protagonists and intense antagonists. And both groups are vocal.” - Alexander Shulgin10

Going by the street name “ecstasy”, not everyone would necessarily consider 3,4-methylenedioxymethamphetamine (MDMA) a medical or psychedelic drug. The public conception of it seems to be that of a stimulant, taken by party-goers at nightclubs and festivals. According to media reports, these party-goers appear to frequently fall victim to adulterated pills and other risks of recreational use, with severe consequences.

Others who have had experiences with the drug or its users might know it by the name ‘hug-drug’, due to its empathogenic effects. But this conception omits the history of MDMA in the psychotherapeutic context, the complexities of its risks and dangers, and most recent scientific findings indicating the usefulness of MDMA as an adjunct to psychotherapy. The complexities of MDMA research will be addressed in this blog post, by sketching out a history of MDMA and its scientific investigations.

Discovery and initial investigation

The history of ecstasy begins in 1912, when chemists at Merck Pharmaceuticals first produced and patented it as an intermediate in a chemical reaction used to manufacture blood clotting agents. After this first description of its chemical formula in 1912, some pharmacological tests were performed at Merck in 1927, though the details of these experiments are unfortunately difficult to track down1. MDMA’s psychological effects in humans were not scientifically investigated until the late 1970s1. This was only done after its apparent use as a street drug, as indicated by police seizures of the substance in the early 1970s2.

In 1978, Alexander Shulgin and David Nichols published a book chapter entitled “Characterization of Three New Psychotomimetics”3, describing the psychological effects of substances chemically related to known psychoactive substances. In this publication, they described MDMA as a drug that “appears to evoke an easily controlled altered state of consciousness with emotional and sensual overtones”3 and compared its effects to cannabis, low doses of MDA, and psilocybin without sensory hallucinations3. These distinct effects of the drug as compared to classic psychedelics later led Nichols to identify it as part of a subgroup of psychedelics specifically prompted by MDMA: the entactogens4.

Popularization and Criminalization

It was Shulgin, too, who introduced MDMA to psychotherapists around the mid-1970s, and who subsequently used it as an adjunct to psychotherapy without formal FDA approval. From the late 70s until the mid-80s, the use of MDMA among therapists slowly but steadily increased, yet no controlled scientific research on its effects in therapy was conducted during this time5. Notably, this was around 10 years after LSD was used in similar underground psychotherapy and subsequently prohibited. As with LSD, over time MDMA increasingly attracted attention for its recreational effects. Some commercial vendors marketed the drug under the street name “ecstasy” for recreational users. Therapists, on the other hand, rather referred to it as “Adam”6,7

With rising popularity amongst recreational users, MDMA did not go unnoticed by politicians and the authorities. First and foremost, in response to Texas senator Lloyd Bentsen’s observation of its widespread use in Texas nightclubs, the Drug Enforcement Agency (DEA) declared their plan to regulate MDMA as a Schedule 1 substance in 19845. They asserted that the substance lacked any recognized medical use. This planned scheduling was immediately contested by a group of mental health practitioners and researchers who requested the hearing of experts in the process of determining the future legal status of the substance. However, in July 1985, the DEA temporarily banned MDMA for one year due to prior findings on the neurotoxicity of its chemical analogue MDMA, as well as its widespread availability. After the hearings, the responsible judge recommended that MDMA be placed in Schedule 3 in May 1986, stating that he believed MDMA had an accepted medical use; this would have allowed for its research and its use in therapy5.

However, “the DEA’s administrator, John C. Lawn, was not convinced […]”5 by the judge’s ruling and the DEA overruled his decision, arguing that MDMA was not a drug regulated by the FDA and therefore had no accepted medical use. Harvard Psychiatrist Lester Grinspoon and Earth Metabolic Design Laboratories (EMDL, a predecessor of the Multidisciplinary Association for Psychedelic Science – MAPS) subsequently filed an appeal based on the FDA-medical-use argument and misconduct of the DEA, which had performed the emergency scheduling of MDMA before getting the formal authorization to do so, and which had overruled the judge’s decision5,8. The appeal was granted, and thus MDMA remained unscheduled.

Simultaneously, multiple articles published in scientific journals were advocating for MDMA’s therapeutic potential. George Greer9, who facilitated many MDMA-assisted therapy sessions, published an overview of the subjective effects reported by patients who took the substance during therapy. Alexander Shulgin10 described a comprehensive summary of MDMA’s chemical background and what was known about its pharmacology. Lester Grinspoon11 outlined the theoretical background underlying the anecdotal evidence for psychedelic-assisted psychotherapy, with a special emphasis on the potential of MDMA. San Francisco based psychiatrist Philip Wolfson6 presented clinical case studies of MDMA-assisted psychotherapy and tried to specify in which situations it may be helpful, and when it might have severe limitations and perils. Moreover, funded by EMDL, Joseph Downing12 published a study on the physiological and psychological effects of MDMA in human volunteers, concluding that “one can only say that MDMA […] has remarkably consistent and predictable psychological effects that are transient and free of clinically apparent major toxicity”12. And,

also funded by EMDL, Charles Frith and colleagues administered MDMA to dogs and rats 13. They stated that “neuropathological changes were not evident in either species”, thereby challenging the concerns about neurotoxicity resembling that of MDA. Despite these attempts to justify the therapeutic use of MDMA, the DEA finally placed the drug in Schedule 1 in March 19885.

After the Schedule 1 Listing

Soon after the scheduling, George Ricaurte et al.14 published a first investigation into the neurological risks of MDMA based on findings in nonhuman primates. This group of Johns Hopkins researchers was the first to show that serotonin depletion, as well as structural changes in the serotonin system, are among the consequences of MDMA consumption. Simultaneously, the recreational use of MDMA in the form of ecstasy pills with electronic dance music started to spread around the globe. Since MDMA was illegal pretty much everywhere, the surge in what was now deemed ‘illegal abuse’ enabled policymakers to provide generous funding to investigate the risks and dangers of the illicit use of the substance.

This risk-centered paradigm was set to dominate MDMA research for the subsequent decades. The bulk of research on the substance’s risks that accumulated over that time was critically examined by Liverpool psychologist Jonathan Cole15, who argues the last 30 years of ecstasy research and its results have to be understood in the context of what he calls the ‘ecstasy paradigm’: Since MDMA has become an illegal drug, its scientific investigation and the public discourse have become subject to moral norms concerning the consumption of drugs. He posits that it became imperative for scientists to show that MDMA is dangerous, which presumably led to multiple flaws in reasoning and methodologies and thereby to biased scientific findings.

For instance, Cole claims a systematic publication bias in the risk-centered literature. He exemplifies this using a situation in which one of his papers, indicating that ecstasy users may not be psychiatrically impaired in the way that has been suggested by others, was rejected. One of the anonymous peer reviewers, whom Cole implicates as part of the problem, commented that he found the data hard to believe15.

Scientific research on the therapeutic effects of MDMA was effectively halted by the Schedule 1 listing. However, organized efforts to enable research into these aspects of MDMA were already made around the time of the scheduling. The aforementioned EMDL was founded to challenge the DEA’s scheduling of MDMA. In response to the Schedule 1 listing of the drug and the lack of evidence to support it, one of the EMDL’s co-founders, Rick Doblin, went on to start MAPS. The idea behind this was to create a non-profit pharmaceutical company which would “facilitate research into the therapeutic uses of MDMA-assisted psychotherapy”8.

However, the political climate remained unfavorable until fairly recently. Throughout the years, further writings resembling and building upon the 1986 journal articles have been published to advocate for substance-assisted psychotherapy, and specifically MDMA-assisted psychotherapye.g. 14–18. And eventually, the first MAPS-funded randomized controlled clinical trial investigating MDMA-assisted psychotherapy was conducted by José Bouso et al.21. Their study, for which they started enrolling patients with post-traumatic stress disorder (PTSD) in 2000, was prematurely shut down in 2002 due to political pressure, leaving 23 out of 29 patients untreated and insufficient data for statistical analysis8,21.

Undeterred, MAPS funded Michael Mithoefer’s22–24 trials in the U.S. and Peter Oehen’s25 trial in Switzerland. Despite minor inconsistencies in the results, possibly due to the small sample sizes, the studies indicated that MDMA-assisted psychotherapy is a promising therapeutic approach for PTSD26,27. Additionally, a recent MAPS-funded study indicates that MDMA-assisted psychotherapy may decrease symptoms of social anxiety in autistic adults28.

As opposed to applied clinical and forensic research, throughout the last ten years MDMA has also increasingly been studied from a more basic scientific perspective. This approach does not focus on the positive or negative effects of MDMA, but on neutrally investigating the effects of the substance in humans. While pharmacological data has already been obtained in the context of forensic science, some fields have only emerged after the 2000s revival of research on MDMA-assisted-psychotherapy. For example, the effects of MDMA on human socio-emotional cognition and behavior have been under investigation since 2009e.g. 29–31. Furthermore, some researchers are performing mechanistic studies in which certain receptors are blocked pharmacologically to illuminate the neurobiology underpinning MDMA's psychological effects e.g. 32–34. Both of these approaches not only expand our knowledge of MDMA and its effects, but also provide unique insights into the neurobiology underlying complex cognitive and affective processes. While these advances may bear less imminent implications for practice, they offer great potential for general scientific advancement and translational research at a later point.

Changing Paradigms – Future Directions

For years, research on MDMA has been limited to investigating the risks of its recreational use. This seems to be mainly due to the limited evidence base on the substance's therapeutic effects at the time of the DEA scheduling. But largely thanks to the persistent work of MAPS, we can now distinguish between several strands of MDMA research. These strands partially correspond to the dual use of the drug in recreational and therapeutic contexts, but recently began to include basic scientific investigations as well. This research seeks to enable not only more precise management of the risks of recreational use and better treatment of mental health conditions, but also to bring general scientific advancement.

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