Clinical Commentary

Biological Psychiatry

Any Questions? A Sober Look at MDMA

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"This is your brain. This is your brain on drugs. Any questions?" With these 12 words the image of sizzling fried eggs was seared into the brains of millions of Americans. The D.A.R.E. era had begun.

The Reagan White House set a clear tone that left no room for evidence or inquiry. The first lady was a leading voice in the War on Drugs: "For the sake of our children, I implore each of you to be unyielding and inflexible in your opposition to drugs." And so, children of the '80s were bombarded with scare tactics and urban legends that masqueraded as "education." Coupled with dog whistles about "inner city crime," drug policy became both rigid and intensely politicized.

This prohibitionist approach stood in contrast to a long history of research on the psychoactive properties of drugs. Freud experimented with cocaine to "untie his tongue." Bill Wilson, co-founder of Alcoholics Anonymous, credited insights from LSD with helping him fight addiction. The CIA, on a more dystopian path, tested a wide range of drugs for mind control and interrogation with its classified MK-Ultra project. This devolved into LSD inexplicably appearing in brothels and bottles of Cointreau as covert dosing of psychedelics became an occupational hazard at the CIA (1).

Amid this frenzy was MDMA (3,4-methylenedioxymethamphetamine). First synthesized in 1912, the drug was largely overlooked until its "rediscovery" in the 1970s by chemist Alexander Shulgin. Shulgin was researching serotonergic amphetamine analogs. He also had an inclination for ingesting his end product. He found its "lightening" effects unique and passed it along to fellow researchers and friends, including retired psychotherapist Leo Zeff. Zeff was so impressed that he abandoned retirement to become MDMA's Johnny Appleseed, spreading it to thousands in the psychotherapy community. Some therapists and patients came to swear by the drug's effectiveness, touting it for enhancing insight without inducing fear.

Their timing was poor. Shulgin and Zeff's work emerged in the wake of the Vietnam War. Anti-war protesting and increasing recreational drug use in hippie and student movements was followed by a tremendous conservative backlash. President Nixon labeled Timothy Leary the "most dangerous man in America" for urging youth to "turn on, tune in, drop out." The government passed the Controlled Substances Act of 1970, thereby creating our current scheduling system and criminalizing unlawful possession. As part of the process, they created a commission with the specific goal of studying cannabis. The committee concluded that cannabis should be decriminalized; instead, bowing to political pressure, it was placed in Schedule I along with LSD and heroin. The motives for this work were carefully calculated and had nothing to do with science. As John Ehrlichman, Nixon's Domestic Affairs Advisor, later described:

> *The Nixon White House… had two enemies: the antiwar left and Black people… We knew we couldn't make it illegal to be either against the war or Black, but by getting the public to associate the hippies with marijuana and Blacks with heroin, and then criminalizing both heavily, we could disrupt those communities. We could arrest their leaders, raid their homes, break up their meetings, and vilify them night after night on the evening news. Did we know we were lying about the drugs? Of course we did. (2)*

For the moment, MDMA escaped government attention. Therapists kept quiet when they used it as "empathy." Meanwhile, the same compound emerged on the rave scene as "ecstasy." Clandestine chemists saw MDMA as a legal alternative that could fill the demand in the recreational market left in the wake of other bans.

As MDMA's popularity grew, society took notice. Fueled by media reports of a dangerous new "club drug," rhetoric became increasingly politically charged, with an emphasis on usage by "college students and gays" (3). During a debate about banning MDMA on the *Donahue* show, researchers announced pre-published reports stating MDA (3,4-methylenedioxyamphetamine) caused brain damage in rats and they extrapolated that MDMA could do the same in humans (3). The published article was less sensational: the study had used repeated, large intravenous doses and the authors noted that the results could not be generalized to typical human ingestion (4). [Much later, a 2002 *Science* paper by the same lead author compounded this false narrative, claiming that common recreational doses of MDMA in primates caused severe neurotoxicity and even death. Though the study was soon retracted—the authors had incorrectly administered toxic doses of methamphetamine, not MDMA (5)—the story had an indelible impact on public perception.]

In the midst of the 1980s fear-mongering, the Drug Enforcement Agency (DEA) set a hearing to rule on the scheduling of MDMA. The judge overseeing the proceedings carefully reviewed all available data. Citing evidence of the drug's therapeutic benefits and relatively low potential for abuse, the judge stated "the findings and conclusions…permit, and indeed require, that MDMA be placed in a schedule other than Schedule I." He concluded that MDMA be placed in Schedule III. Despite the evidence, the DEA "just said no" and MDMA was designated as a Schedule I substance with "no acceptable medical use." The ruling blocked all public funding for clinical MDMA research. Politics trumped science.

Over the ensuing decades, with a resurgence of interest and with private funding, several groups obtained exemptions to reopen the question: does MDMA have clinically useful properties? And, at an even more basic level, how does it work?

MDMA's mood-elevating effects have often been linked to serotonin release, and its sense of arousal related to

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dopaminergic and noradrenergic properties. These ideas aligned nicely with early monoaminergic models of depression. However, much like models of antidepressant mechanisms (6), it seems that secondary processes may be even more relevant. Serotonin's role in downregulation of amygdalar hyperactivity may be one important component, but a new connection was made from an initially unrelated line of neuroscience research.

More than 30 years after MDMA was placed in Schedule I, Gul Dölen and her research team were interested in one of the hottest topics in social neuroscience: neuroplasticity and early development. As part of their work, they wanted to explore the role oxytocin might play in social development. Classically thought of in the context of obstetrics, oxytocin was garnering attention for studies linking it to everything from autism to orgasm. Dölen's team was interested in the hormone's role in critical window periods—discrete times during which individuals have a heightened ability to learn. The team faced a problem, though: oxytocin does not readily cross the blood-brain barrier. But it turns out, there's a trick. Separate research had shown that MDMA administration leads to the downstream release of oxytocin in the brain. So Dölen's team used MDMA to attempt to reopen critical windows of social reward learning: and it worked (7). MDMA helped mature mice to learn social behaviors normally only learned during youth. They also confirmed that MDMA's effects were dependent on the oxytocin pathway.

But there was another crucial detail: the drug didn't work on its own. Adult mice given MDMA but kept in isolation did not learn new behaviors; the drug only worked to induce plasticity when given in conjunction with social and environmental input (7). While Dölen's work was in rodents, it seemed to recapitulate what Shulgin and Zeff had promoted 40 years before—MDMA might facilitate the learning that occurs though social interaction, such as psychotherapy.

The potential applications to modern medicine are clear. For example, PTSD is a disease of disordered memory and the current gold standard treatments (such as prolonged exposure) are those that address the overconsolidation of the fear response. Substance use disorders are also diseases of disordered (reward) learning. It is possible that existing therapies could be augmented with a drug like MDMA to facilitate new learning, with oxytocin acting as a key mediator.

There may be more to the role of oxytocin than its effects on neuroplasticity and social behavior. Trauma therapies can trigger intolerable levels of distress in some individuals, thereby contributing to high treatment dropout rates. Oxytocin also has receptors throughout the autonomic nervous system that allow it to activate parasympathetic tone and attenuate stress (8). Which is to say: MDMA leading to increased parasympathetic activation (via oxytocin) along with increased arousal may lead to improved engagement by making the distress of therapy easier to tolerate.

Times have changed and science is finally regaining footing. Over the past decade, new research is once again exploring potential therapeutic uses of psychedelics (9). Not all studies have been positive. But some data are encouraging. For example, MDMA-assisted therapy has now completed the first positive phase 3 study (10). Unfortunately, decades of research have been lost to politics co-opting the narrative, sacrificing both social justice and medical progress.

So, "This is your brain on drugs. Any questions?" Well… yes…many. The field has progressed from cracking open eggs to cracking open critical learning windows. The time is ripe to rigorously study historically banned substances. Such questions are needed to gain more sober insights into these substances' true safety profile and therapeutic potential.

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