MDMA for the treatment of mood disorder: all talk no substance?

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Abstract

Background: Unipolar depression is the third highest contributor to the global burden of disease, yet current pharmacotherapies typically take about 6 weeks to have an effect. A rapid-onset agent is an attractive prospect, not only to alleviate symptoms before first-line antidepressants display therapeutic action, but as a further treatment option in nonresponsive cases. It has been suggested that 3,4-methylene-dioxymethamphetamine (MDMA) could play a part in the treatment of depression, either as a rapid-onset pharmacological agent or as an adjunct to psychotherapy. Whilst these hypotheses are in keeping with the monoamine theory of depression and the principles surrounding psychotherapy, explicit experimental evidence of an antidepressant effect of MDMA has rarely been established.

Aims: To address the hypothesis surrounding MDMA as a rapid-onset antidepressant by examining pharmacological, psychological and behavioural studies. We consider whether this therapy could be safe by looking at the translation of neurotoxicity data from animals to humans.

Method: A literature review of the evidence supporting this hypothesis was performed.

Conclusions: The pharmacology of MDMA offers a promising target as a rapid-onset agent and MDMA is currently being investigated for use in psychotherapy in anxiety disorders; translation from these studies for use in depression may be possible. However, experimental evidence and safety analysis are insufficient to confirm or reject this theory at present.

Keywords: MDMA, monoamine theory, mood disorder, psychotherapy, rapid-onset antidepressant

Introduction

3,4-Methylene-dioxymethamphetamine (MDMA), the active component of 'ecstasy', is a recreational drug which has recently been proposed to exhibit antidepressant properties [Riedlinger and Montagne, 2001; Sessa and Nutt, 2007]. This postulate is based on the acute pharmacology of MDMA and is consistent with the hallmark theory of depression, the monoamine hypothesis [Krishnan and Nestler, 2008]. MDMA rapidly increases availability of extracellular 5-hydroxytryptamine (5-HT) at the synapse, mirroring the action of commonly prescribed antidepressants. However, current first-line treatments for depression, such as selective serotonin reuptake inhibitors (SSRIs), typically take about 6 weeks to produce optimum therapeutic change [Frazer and Benmansour, 2002]; MDMA could offer instantaneous relief. This rapid onset is an attractive prospect for treatment-resistant depression (TRD), where currently the only therapeutic option is electroconvulsive therapy (ECT). Although there is a theoretical basis, at present experimental evidence of antidepressant action of MDMA is low, with just one rodent [Majumder *et al.* 2011] and one volunteer study [Majumder *et al.* 2012] suggesting direct rapid-onset antidepressant action.

MDMA is a controlled substance in most countries, typically in the most restrictive category (Class A in the UK). Despite this, MDMA is already in clinical trials for anxiety disorders such as post-traumatic stress disorder (PTSD), as an adjunct to psychotherapy where it is thought to assist therapy sessions by strengthening the

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therapeutic relationships between patient and therapist [MAPS, 2015; Mithoefer *et al.* 2011, 2013; Oehen *et al.* 2013]. Psychotherapy, in the form of cognitive behavioural therapy (CBT), is one of the most effective treatments for depression, indicating that the translation of MDMA-assisted therapy to depression may also be beneficial.

To date, experiments using MDMA have been of limited scope, in part due to its Class A scheduling, as well as concerns over its safety and neurotoxicity profile. Through recreational use, it has garnered a reputation for being dangerous in the media, with reports focused on the rare deaths of young adults; and in the scientific literature through demonstration of neurotoxicity in animals. In humans, MDMA overdose can produce hyperthermia, with subsequent muscle break down resulting in hyperkalaemia and organ failure [Carvalho *et al.* 2012]. However, the doses required for these effects are excessive and thus reports of death solely from MDMA overdose are scarce; MDMA is more commonly linked to death as a contributing factor in a polydrug environment [Kaye *et al.* 2009]. To date, there are no published studies demonstrating neurotoxicity of repeated low dose MDMA in drug-naïve volunteers; indeed this regimen is in use in PTSD trials and has been postulated to have antidepressant activity [Sessa and Nutt, 2007].

Animal studies highlight physiological and psychological changes that occur after MDMA exposure, but these studies are limited, employing aggressive dose regimes over intense time periods that do not reflect patterns of human recreational use or those utilized in clinical trials [Mithoefer *et al.* 2011, 2013; Oehen *et al.* 2013]. Data from recreational users are also inadequate, restricted by retrospective design that cannot rule out premorbid differences, as well as reliance on self-reported variables of time and dose. Additionally, such data are confounded by polydrug use and ambiguity over whether 'ecstasy' tablets contain MDMA; a recent government report states that 'most ecstasy tablets sold in the UK do not contain MDMA [Jones *et al.* 2011]. If MDMA is to be assessed for its antidepressant properties, there is an urgent need to eliminate equivocal data, as interpretation and relevant translation to patient populations is currently impossible. In this article we examine the conclusions of both animal and human literature to assess whether MDMA could prove a safe and effective therapy for TRD.

MDMA pharmacology

Positive indications

MDMA is an amphetamine derivative, capable of crossing the blood–brain barrier to the central nervous system, where its major substrates are the vesicular and presynaptic monoamine transporters [Elliott and Beveridge, 2005]. Early work identifying MDMA substrates, using *post mortem* brain material, or *in vitro* tissue samples, concluded that MDMA acts to reverse transport across these proteins, inducing a rapid, dose-dependent, nonexocytic monoamine release into the synapse [Schmidt, 1987; Rudnick and Wall, 1992; Rothman and Baumann, 2002]. These finding have been recapitulated in conscious rats [Baumann *et al.* 2005].

Of the monoamines, MDMA has highest efficacy for 5-HT release *via* the serotonin reuptake transporter (SERT) [Steele *et al.* 1987; Elliott and Beveridge, 2005]. Thus, MDMA acts to increase 5-HT availability in the acute setting, as SSRIs do chronically. Indeed, many of MDMA's effects are abolished in SERT-deficient mice [Bengel *et al.* 1998; Fox *et al.* 2007], as well as by SSRIs, which act as competitive antagonists to SERT [Schmidt and Taylor, 1987]. In humans, SSRIs also diminish the effects of MDMA [Liechti and Vollenweider, 2000], an important consideration when thinking about use as a rapid-onset antidepressant or augmentation therapy. That is, giving MDMA in conjunction with commonly used antidepressants may prevent the therapeutic effects of MDMA, due to substrate competition [Hysek *et al.* 2012]. In addition to monoamine modulation itself, MDMA-induced 5-HT release acts to increase oxytocin in humans [Dumont *et al.* 2009]. Oxytocin characteristically precipitates prosocial behaviours and an improved ability to infer the mental state of others [Domes *et al.* 2007]; this has the potential to offer a gateway to successful psychotherapy.

Negative indications

Following acute MDMA-induced 5-HT release from serotonergic terminals, in conjunction with inhibition of 5-HT reuptake, marked depletions in 5-HT and its metabolite, 5-hydroxyindoleacetic acid (5-HIAA), have been reported in *post mortem* brain tissue of animals and humans [Schmidt *et al.* 1986], as well as *in vivo* from cerebrospinal fluid (CSF) measurements [Ricaurte *et al.* 1990;

Taffe *et al.* 2003]. This does not bode well for use as an antidepressant following the monoamine theory of depression. Yet, these data are not definitive; rodent studies drawing such conclusions have used single doses, more than 10 times greater than an average recreational dose [Schmidt *et al.* 1986] or multiple high doses in rapid succession [Wallinga *et al.* 2011]. Primate data follow similar regimes [Ali *et al.* 1993].

In order to make measurements of CSF markers relevant, recreational doses need to be paralleled, as evidence suggests there is no need for interspecies scaling [Baumann *et al.* 2007]. Studies investigating CSF 5-HIAA concentrations in recreational users [Ricaurte *et al.* 1990; McCann *et al.* 1994] have consistently reported decreased levels of the metabolite, repeating animal literature, but these demonstrations come from polydrug users with unknown dosing. Tryptophan hydroxylase (Tph) activity also diminishes post-MDMA exposure [Bonkale and Austin, 2008, Schenk *et al.* 2013], although these measurements have rarely exceeded 2 weeks in studies. Furthermore, a recent rodent study found that diminished Tph after MDMA administration is transient and can recover in all brain regions [Adori *et al.* 2011].

Human data on changes in Tph typically come from *post mortem* tissues and these studies lack statistical power. One case report demonstrates that Tph was severely decreased in an autopsied brain of a 'chronic' MDMA user. Yet, this report also indicates that the subject took MDMA 4–5 nights per week, for 3 years prior to death and, on the weekend, would ingest 6–8 tablets [Kish *et al.* 2010]. Hair analysis further confirmed chronic cocaine use in this subject. Thus, the results represent an atypical pattern of heavy use, which would be unlikely to given therapeutically and are confused by polydrug use.

Thus, although current studies are heavily confounded, the evidence currently highlights a discrepancy between the acute and chronic pharmacology of MDMA. Acutely, MDMA works to increase 5-HT availability, suggestive of rapid-onset antidepressant properties and positive changes to emotion, but this transient effect may be accompanied by later depletions of 5-HT. However, studies examining long-term effects are inadequate and thus it cannot be concluded that MDMA significantly depletes 5-HT stores at doses that would be used therapeutically.

MDMA neurotoxicity

Reduced levels of 5-HT and its metabolites in brain tissue and the CSF have been interpreted to indicate that MDMA is neurotoxic, although definitive data must come from histological validation of neurodegeneration [Kaye *et al.* 2009]. To assess this *in vivo*, reduced SERT density is thought to represent neurotoxicity [Urban *et al.* 2012]. Incidentally, a low SERT density is also associated with depression [van Eijndhoven *et al.* 2011]. In humans, such investigations use imaging techniques such as positron emission tomography (PET), which rely on radioligands to label SERT. Currently, [^{11}C] 3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)benzonitrile (DASB) is considered the most specific ligand [Frankle *et al.* 2004].

[^{11}C]DASB studies on recreational users indicate global SERT depletion, in part, positively correlated with MDMA consumption, but also that SERT densities have a capacity to recover, at least in subcortical regions [McCann *et al.* 2005]. These results are notable but incomplete because they were obtained retrospectively. Attempts to overcome these limitations include recruitment of 'chronic' users, in the hope that they have had at least some exposure to MDMA, and hair analysis, allowing levels of MDMA to be verified up to approximately 3 months prior to testing. For example, in one study comparing SERT levels between MDMA users and MDMA-naïve controls, hair analyses confirmed the subjects' drug history and 'chronic' MDMA users were defined as taking the substance for a mean of 4 years, taking 1–2 tablets every 2 months [Kish *et al.* 2010]. The authors found that SERT binding was significantly lower in the cerebral cortex and hippocampus, and correlated to the time and dose of drug use. Converging on similar conclusions, one of the most recent [^{11}C]DASB studies found decreased SERT binding in cortical regions in MDMA users [Urban *et al.* 2012]. Depletion was correlated with increases in 5-HT$_{2A}$ receptor availability, a postsynaptic 5-HT receptor known to upregulate in response to chronic 5-HT depletion, suggesting that the brain is adapting to insult.

Other studies have extended the 5-HT$_{2A}$ data, repeating the findings that 5-HT$_{2A}$ receptors are upregulated in MDMA users [Benningfield and Cowan, 2013]. However, the perceived receptor deficiencies cannot be attributed to MDMA alone in these subjects. Hence, it is impossible to determine what dose of MDMA alters serotonergic

function, accompanied by neurotoxicity, post exposure. Furthermore, behavioural and biochemical analysis must be coupled to determine whether these changes have a detrimental effect on MDMA users. If no significant behavioural effects accompany these changes, perhaps we need to question whether these changes are a problem. To address this, a prospective volunteer study that can be tightly regulated is desirable to examine both biochemical and behavioural differences after low-dose MDMA.

Despite MDMA passing safety measures for its use in clinical trials of PTSD, we believe that until the discrepancies in neurotoxicity data are resolved, it is unlikely that MDMA will be explored as a rapid-onset antidepressant because of the emphasis in both depression pathophysiology and MDMA neurotoxicity on 5-HT. MDMA is the second most popular illicit substance in Europe, peaking in popularity in the 1980s, and thus if MDMA use posed a chronic, detrimental effect, a resultant epidemic should emerge shortly. As of yet this does not appear to have surfaced and thus it might be hypothesized to be unlikely that MDMA has a noticeable lasting effect.

Psychological effects of MDMA

Animal studies

Animal studies carried out to address the psychological impacts of MDMA are often nontranslatable to therapeutic settings because of limitations outlined previously. Following a 10mg/kg dose of MDMA for 10 days in rats, measures of anxiety-like behaviours, such as open-field ambulation, indicate an increase in anxious phenotypes 3 months later [Kolyaduke and Hughes, 2013]. A dose of 5mg/kg of MDMA given to rats 4 times in 4 hours, on 2 consecutive days, diminished responses on the forced swim test and increased immobility up to 12 weeks post-MDMA exposure, indicating long-term negative behavioural changes [Thompson *et al.* 2004]. This study also analysed levels of 5-HT and 5-HIAA *post mortem*, with both being decreased in cortical areas of MDMA-treated rats. This can be interpreted as MDMA-induced chronic depletion of 5-HT, leading to anxious or depressed phenotypes. However, aggressive dosing was employed; these effects may not be seen with a modest dosing regimen.

Primate data show that, although CSF depletions of up to 93% in 5-HT and around 50% 5-HIAA are seen up to 1 year after a brief, high-dose MDMA regime [Domes *et al.* 2007], no behavioural changes, such as memory and reaction time, accompany these apparently drastic reductions. However, it is unfortunate, for the purposes of this debate, that this study did not also assess mood.

Human data

Numerous studies have compiled data from recreational users to investigate the relationship between MDMA and mood in humans. In one self-reported study, it was stated that the feeling of depression post-MDMA exposure in a cohort of 20 'ecstasy' users was 55% [Davison and Parrott, 1997]. In a larger study, 52 frequent 'ecstasy' users were questioned, and the prevalence of depression reported was just 4% [De Almeida and Silva, 2003]. It is difficult to determine which figure is more representative as both studies used retrospective designs lacking biochemical analysis to confirm MDMA or other drug use. Furthermore, in humans, there is an argument that the environment in which MDMA is taken, rather than MDMA itself, causes negative changes to long-term mood, a factor that these self-reported studies do not consider. Indeed, it is suggested that reduced quality of sleep following recreational MDMA use, rather than the use itself, can lead to depression, anxiety and aggression [Scott *et al.* 2013].

Prospective studies have also been conducted, attempting to clarify whether MDMA use precipitates depression, or whether the drug is used recreationally as self-medication. One such study investigated behavioural outcomes of MDMA use in an initially MDMA-naïve population who were likely to use MDMA in the near future [De Win *et al.* 2006]. These volunteers underwent a number of behavioural tests over a mean period of 16 months, with data suggesting that premorbid depression did not predict MDMA use. In addition, this study found that depression post-MDMA was not significantly increased. However, these findings are not consistent across the prospective study literature [Lieb *et al.* 2002; Huizink *et al.* 2006; Briere *et al.* 2012].

A large Dutch population study explored the relationship between behavioural traits exhibited by school children and their future MDMA use, assessed 14 years later *via* questionnaire [Huizink *et al.* 2006]. The work found that the children

who had fulfilled the criteria for anxious or depressed childhood behaviours were significantly more likely to used MDMA as they grew up and into young adulthood. A 4-year prospective study of 14–24 year olds from Munich demonstrated that ecstasy users had a 3-fold odds increase in the presence of mental disorders compared with nondrug users and a 2-fold odds increase compared with non-ecstasy users [Lieb *et al.* 2002]. As a prospective study the temporal nature of this relationship was investigated and it was demonstrated that, in 80.4% of ecstasy users with mental disorders, the presence of mental illness predated ecstasy use. Major depressive disorder was associated with increased ecstasy use and, within the cohort of ecstasy users with comorbid depression, the diagnosis of depression predated ecstasy use in 44.5%. In both these studies the authors proposed that these data were evidence that mental illness leads to increased rates of ecstasy use, in fitting with a hypothesis of self-medication. Differences between prospective studies still leave ambiguity, likely due to confounding factors such as polydrug use, dose and compound uncertainty.

Research into MDMA and its biochemical and/or behavioural effects on healthy volunteers now has considerable statistical power, with about 900 people having partaken in clinical trials. Kirkpatrick and colleagues undertook an analysis of data of the effects of MDMA across three different laboratories, with 220 healthy volunteers [Kirkpatrick *et al.* 2014a]. They demonstrated consistent subjective effects, as well as physical changes. The subjective effects were assessed using visual analogue scales and covered perception of a drug effect, liking of drug effect, closeness to others and feelings of anxiety. Significant positive shifts were demonstrated on each of these factors. Physical changes related to an increase in both heart rate and blood pressure, resulting in a significant cardiovascular profile, which may prove problematic for patients in older age and those with pre-existing medical health problems. The overarching conclusion of this work is that the measured subjective and physical effects of MDMA are reproducible, irrelevant of population, demographic and experimental methodology.

In 1998, Vollenweider and colleagues safely conducted the first trial examining the effects of MDMA on nonpatient volunteers [Vollenweider *et al.* 1998]. Recently, a number of studies have furthered this work to characterize the acute effects of MDMA in a controlled environment [Hartman *et al.* 2013; Carhart-Harris *et al.* 2014a, 2014b; De Sousa Fernandes Perna *et al.* 2014; Frye *et al.* 2014; Hysek *et al.* 2014; Kirkpatrick *et al.* 2014b, 2014c; Kuypers *et al.* 2014; Schmid *et al.* 2014, 2015; Seibert *et al.* 2014; Spronk *et al.* 2014; Wardle and De Wit, 2014; Yubero-Lahoz *et al.* 2014; Clark *et al.* 2015]. Two papers of note, examining the psychological effects of MDMA were published by the groups of Nutt and De Wit respectively [Carhart-Harris *et al.* 2014b; Frye *et al.* 2014]. Nutt's group looked at the effects of a modest MDMA dose on the recall of emotionally important memories, using functional magnetic resonance imaging (fMRI) and subjective ratings [Carhart-Harris *et al.* 2014a. De Wit's group investigated the effects of MDMA on the perception of social rejection using a computer simulated task and subjective ratings [Frye *et al.* 2014a]. In both studies, MDMA was shown to enhance positivity. In the work by Nutt's group, participants reported that during the use of MDMA, worst memories, such as the death of a close friend, were significantly less negative, whilst favourite memories were more positive, vivid and emotionally intense. In the study by De Wit's group, enhanced positivity is demonstrated by a decreased subjective response to rejection. These two papers address differing areas of MDMA's psychopharmacology, with effects of enhanced positivity apparently appearing consistent across both autobiographical recollection and contemporaneous subjective experience. These findings are highly supportive of the putative use of MDMA in depression for elevating mood, as well as further supporting the use of MDMA as an adjunct to psychotherapy. A modulation enabling increased positivity has the potential to increase engagement in the therapeutic process, to assist in the exploration of the underlying cognitions and to create a platform for subsequent behavioural change.

These studies have paved the way for exploration of the acute effects of MDMA on psychology. For the purposes of an antidepressant therapy, it will be important in the future to explore whether the positive changes in psychology demonstrated can persist beyond the duration of the acute actions of MDMA. In addition, translation to patient groups will need to be addressed. We have found one study looking at the effects of MDMA on mood in a putative target population [Majumder *et al.* 2012], which reported that in a population of MDMA

users, with and without a predisposition of depression, the administration of the drug decreases depressive symptoms. The authors argue that this effect could underlie the popularity of MDMA as a form of self-medication; we would argue that this further supports the hypothesis that MDMA may provide a helpful therapy in depression.

Recreational drugs as clinical therapies

Rapid-onset antidepressants

In the 1940s, the first antidepressant, amphetamine, was used for its rapid-acting pharmacology. In his excellent book, *On Speed: The Many Lives of Amphetamine*, Rasmussen discusses the history of amphetamines and their rise to fame as wonder drugs that claimed to cure a whole host of ailments from obesity to mood disorders [Rasmussen, 2008]. Today the use of amphetamine has clearly fallen out of vogue, in part due to the prolific side effects observed from prescription and their highly addictive nature that led to the patterns of abuse that built up around them. Taboo now shrouds the conversion of illicit substances to clinical therapy; nevertheless, ketamine is in a number of clinical trials for TRD [Murrough and Charney, 2012]. Ketamine's therapeutic use in anaesthesia ensures safety margins are established, but it is still significant that it is being considered as a rapid-onset antidepressant. Many trials of ketamine as a novel antidepressant have taken place in the past year, including a small naturalistic open label study by Diamond and colleagues looking at the efficacy and safety of delivering ketamine treatment within an NHS clinic setting [Diamond *et al.* 2014]. The model used a regime of once weekly intravenous (IV) doses of ketamine for 3 weeks, followed by twice weekly doses for a further 3 weeks, demonstrating a potential model for the safe clinical use of controlled substances which could be applied to MDMA.

Initial evidence supports ketamine's role as a therapy for TRD, but this substance is markedly psychotropic, which may not be desirable for severely ill patients. MDMA is not overtly psychotropic and thus may provide a more attractive therapy. Alternatively, specific analogues to these drugs, lacking unwanted effects, can be developed. One group has synthesized a ketamine analogue for use in TRD [Burgdorf *et al.* 2013] and UWA-101, an MDMA analogue, has also been developed for use in Parkinson's disease. UWA-101 apparently lacks cytotoxicity in primates [Johnston *et al.* 2012]. This could be applied to TRD if the monoaminergic actions of MDMA are decreed to be antidepressant as a designer agent will be less controversial and neurotoxic.

Psychotherapy adjuncts

In the middle of the last century, the precedent was set for the use of psychostimulants as rapid acting antidepressants and a simultaneous interest into the use of psychedelics as adjuncts to psychotherapy developed. In 1967, Naranjo and colleagues published a paper on MDA, a substance structurally related to MDMA, and its potential as an adjunct to psychotherapy on the basis of its ability to heighten affect, increase emotional empathy and increase self-insight, without the distracting perceptual alterations of LSD [Naranjo *et al.* 1967]. In 1986, Grinspoon and Bakalar discussed the history of drug use for the enhancement of psychotherapy and highlighted MDMA as one of the most promising agents of interest [Grinspoon and Bakalar, 1986]. Modern trials of MDMA as an augmentation strategy in cognitive therapies have been initiated with treatment-resistant PTSD patients. PTSD is an anxiety disorder, related and often comorbid with depression, and the protocols from the groups researching the efficacy of MDMA assisted psychotherapy in PTSD could be translated into work on depression. Current protocols consist of a number of MDMA-assisted sessions interspersed with nondrug based psychotherapy sessions, with an overnight inpatient stay following MDMA assisted-sessions to ensure safety [Oehen *et al.* 2013].

It is worth considering that many patients undergoing psychotherapy are on a variety of psychotropic medications and some data suggest that current antidepressants combined with CBT may have reduced effects on outcome. SSRIs negatively affect amygdala function, which is thought to be one of the structural targets of psychotherapy [Browning *et al.* 2011]. Episodic memory, mediated in part by the amygdala, is thought to be impaired in depression and hyperactive responses in the amygdala, to neutral stimuli, are well-documented in depressed subjects [Nestler *et al.* 2002]. MDMA acutely reduces activity in the amygdala [Gamma *et al.* 2000], suggesting that it may help overcome the cognitive insufficiencies linked to depression in addition to correcting monoamine imbalances. However, whether a reduction in amygdala function, as a result of MDMA exposure, affects psychotherapy outcomes, is unknown.

Conclusion

MDMA has the potential to act as a rapid-onset antidepressant *via* its modulation of the 5-HT system and as an augmentation strategy in cognitive therapy. Acutely, MDMA acts to increase extracellular 5-HT availability, portraying an ideal antidepressant agent according to the monoamine hypothesis. A single rodent study has confirmed this acute effect, but use as an antidepressant is restricted by inadequate experimental evidence and safety uncertainties. A precedent for the safe use of MDMA has been set by its use in clinical trials of PTSD, but a more concrete analysis needs to be resolved through human volunteer studies. Large doses appear neurotoxic in animals, thus small doses of subrecreational values, are most appropriate for use in initial trials. A preliminary study to assess safety would need a prospective design, measuring outcomes of therapeutic doses, in drug-naïve volunteers, using PET with [^{11}C]DASB to measure neurotoxicity, in conjunction with psychological tests of emotions linked to 5-HT dysfunction. Once a safety profile and therapeutic index are concluded, the next step will be to look definitively at the antidepressant action of MDMA. There is no doubt that MDMA acutely causes feelings of empathy in almost all users. However, if antidepressant properties are tested, it should be remembered that when healthy volunteers are administered SSRIs, noticeable effects on mood are not recorded and thus it is important to emphasize studies on patients rather than healthy volunteers. In conclusion, the data from PTSD trials of MDMA assisted psychotherapy set a promising precedent that can likely be applied to depression. The use of MDMA as a standalone rapid-onset antidepressant is theoretically well-grounded, but lacks proof of concept.

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