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Invited review

Why MDMA therapy for alcohol use disorder? And why now?

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ABSTRACT

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 were associated with Lysergic acid diethylamide (LSD)-assisted psychotherapy to treat what was then called, alcoholism. But results were varied and psychedelic therapy with LSD and other 'classical' psychedelics fell out of favour in the wake of socio-political pressures and cultural changes. A current revisiting of psychedelic clinical research is now targeting substance use disorders – and particularly alcohol use disorder - again. 3,4-Methylenedioxymethamphetamine (MDMA)-assisted psychotherapy has never been formally explored as a treatment for any form of substance use disorder. But in recent years MDMA has risen in prominence as an agent to treat posttraumatic stress disorder (PTSD). With its unique receptor profile and a relatively well-tolerated subjective experience of drug effects when used clinically, MDMA Therapy is ideally suited to allow a patient to explore and address painful memories without being overwhelmed by negative affect. Given that alcohol use disorder is so often associated with early traumatic experiences, the author is proposing in a current on-going UK-based study that patients with alcohol use disorder who have undergone a medical detoxification from alcohol might benefit from a course of MDMA-assisted psychotherapy.

Contents

1. Introduction: the clinical and social burden of alcohol addiction

Although drinking alcohol is a widely socially acceptable behaviour and many people drink without experiencing problems, approximately 24% of the adult population of England consume alcohol in a way that is harmful and 6% of men and 2% of women meet the diagnostic criteria for alcohol use disorder (NICE guidelines on Alcohol Use Disorders, 2011). The disorder is characterised by withdrawal symptoms on cessation of alcohol, drinking to avoid withdrawal symptoms, tolerance and the persistent desire to drink despite negative consequences (APA, 2013). Alcohol use disorder

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related illness and injuries cause significant social impacts to family, friends and the wider community. Sufferers frequently present with high levels of depression, anxiety and social exclusion and report using alcohol as a form of self-medication (Leeies et al., 2010). Many patients with alcohol use disorder have a history of psychological trauma (Stewart, 1996) and there is an association between the disorder and PTSD (Spates and Souza, 2007).

Considering related health disorders, crime, anti-social behaviour, accidents, loss of productivity and domestic problems, the Department of Health estimates that alcohol use disorder is now costing around £20 billion a year in England alone (HM Government 2012).

2. Current pharmacological and psychotherapeutic options for alcohol use disorder

There are many different sorts of treatments for alcohol use disorder, which reflects the vast differences between patients, severity of disease and multiple confounding psychosocial factors involved. In 2013, almost 200,000 items of medication were prescribed in the UK for the treatment of alcohol use disorder at a cost of £3.13 million, and in 2012 there were 6490 alcohol-related deaths (HSCIC, 2014).

Licensed pharmacological options include acamprosate, disulfiram, naltrexone, nalmafene and benzodiazepines. The glutamate antagonist acamprosate and the competitive opioid antagonists naltrexone and nalmafene are used to reduce the incidence of cravings (Rösner et al., 2010; Soyka and Rösner, 2008; Paille and Martini, 2014). Disulfiram deters use by producing an unpleasant physical reaction if alcohol is taken (Krampe et al., 2006) and benzodiazepines are commonly prescribed as part of an alcohol detoxification programme (Lingford-hughes et al., 2012).

There are a range of psychosocial interventions but the efficacy of current available treatments is far from satisfactory, with high rates of relapse. A systematic review of 361 controlled studies of both pharmacological and psychotherapeutic treatments ranked 46 interventions according to rates of abstinence achieved. The Brief Intervention approach ranked highest and Motivational Enhancement Therapy ranked second. Pharmacotherapy with acamprosate and naltrexone ranked third and fourth respectively (Miller and Wilbourne, 2002). A large prospective study identified 3-year abstinence rates for 12-step facilitation, (TSF) at 36%, Motivational Enhancement Therapy (MET) at 27% and Cognitive-behavioural Coping Skills (CBT) clients at 24% (Project MATCH Research Group, 1998). A more recent review evaluated the efficacy of relapse prevention medications in various combinations with behavioural treatment, indicating that both naltrexone and acamprosate show only minor positive effects in relapse prevention, and only when used in conjunction with well-delivered psychosocial interventions (Anton et al., 2006), which for alcohol use disorder have notoriously high drop-out rates of between 50 and 75% (Jefferson, 1991). Some studies describe 12-month relapse rates after treatment of around 60% at 12-months (Evren et al., 2010) and up to 80% at 3 years (Moos and Moos, 2006).

In conclusion, despite the highly significant clinical, social and financial burden of alcohol use disorder our treatments are far from satisfactory. In this context, in recent years there has been a significant revisiting of research studies exploring the possible role for an innovative approach with psychedelic-assisted psychotherapies for alcohol and other substance use disorders (Sessa and Johnson, 2015).

3. The history of psychedelics in treating substance use disorders

Since the earliest days of psychedelic research in the 1950s, alcohol use disorder has been a recognised target for psychedelic-drug assisted therapy; the theory being that an intense, drug-induced spiritual/mystical peak experience could be honed as method of inducing sobriety (Sessa, 2017a). LSD-assisted psychotherapy was explored with varying rates of success, but there was great heterogeneity between the studies carried out. Early uncontrolled studies showed abstinence rates of between thirty and fifty percent (McLean et al., 1961; Kurland et al., 1967; Ditman and Bailey, 1967; Rydzynski et al., 1968). Some researchers were sceptical of the claims of early researchers and found no significant differences in drinking habits between the randomized groups (Smart et al., 1966; Johnson, 1969) or a lack of lasting improvements (Kurland et al., 1971; Faillace et al., 1970). However, in 2012 a meta-analysis paper reviewed six randomized trials of LSD-for-alcohol use disorder from the 50s and 60s, controlling for the heterogeneity of the early studies, and demonstrated generally favourable results, with 59% of the LSD-treated participants significantly improved compared to 38% of the controls (Krebs and Johansen, 2012). In the 1950s, Bill Wilson, the founder of Alcoholics Anonymous, underwent several LSD-assisted psychotherapy sessions himself and concluded:

> *"It is a generally acknowledged fact in spiritual development that ego reduction makes the influx of God's grace possible … So I consider LSD to be of some value to some people, and practically no damage to anyone."* (Hartigan, 2000).

Nevertheless, in the context of the prohibition of psychedelics, most research had halted by the 1970s.

4. Contemporary psychedelic research for addictions

A team in Russia in the 1990s, driven by the theory behind the 1950s and 1960s studies, investigated the potential role for Ketamine-assisted psychotherapy for both alcohol and opiate use disorders. Placebo-controlled studies on more than 1000 patients showed Ketamine psychotherapy produced total abstinence for more than one year in 66% of the alcoholic patients compared to 24% of the control group (Krupitsky and Grinenko, 1997). A revisiting of Ketamine therapy for treating alcohol use disorder is currently underway in Exeter, UK (Morgan, 2017a).

Psychedelic psychotherapy as a treatment for substance use disorders was reviewed in 2012 in a paper by Michael Bogenschutz and Pommy, 2012. Bogenschutz subsequently carried out a single-group proof-of-concept study on 10 volunteers with alcohol use disorder. Participants received two doses of psilocybin in combination with 12 weeks of outpatient psychosocial treatment including Motivational Enhancement Therapy. Results showed abstinence increased significantly following psilocybin administration and the gains were maintained at follow-up to 36 weeks (Bogenschutz et al., 2015).

Another recent psychedelic-assisted research study for treating other substance use disorders was a small psilocybin-assisted psychotherapy pilot study for nicotine use disorder, which produced abstinence rates from cigarette smoking that far exceeded those of current available nicotine cessation treatments (Johnson et al., 2014). The psychedelic compound ayahuasca has also been explored as a treatment for several different substance use disorders (Loizaga-Velder and Verres, 2014), with one Canadian study showing significant results for ayahuasca improving abstinence maintenance from cocaine use disorder (Thomas et al., 2013).

To date there have been no published studies proposing MDMA Therapy as a treatment for any substance use disorders. But the author is currently carrying out a safety and feasibility study, postulating that MDMA-assisted psychotherapy could be useful in

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treating alcohol use disorder through its capacity to enhance the psychotherapeutic process and treat underlying psychological trauma. In contrast to the psilocybin-assisted psychotherapy for alcohol use disorder by Bogenschutz, described above, the proposed MDMA-assisted study will be conducted upon more severe, physically-dependent daily drinkers, who will undergo a medical detox from alcohol before starting the psychotherapeutic course of sessions.

5. How MDMA therapy works

In discussing the mechanisms of action of MDMA it is important to stress that there remains a lack of scientific consensus around it's pharmacology. The known pharmacology of MDMA, which has been elegantly described in the past as "messy" (Ray, 2016), means that attempts to subsequently relate it's pharmacology to predictable psychological effects – and, furthermore, how these effects might impact on MDMA-assisted psychotherapy - is even more complex. Nevertheless, an attempt to reflect on this challenge is postulated below.

MDMA is a ring-substituted phenethylamine that exerts is effects through promoting raised levels of serotonin, dopamine and noradrenaline. Increased activity at 5-HT_{1A} and 5-HT_{1B} receptors reduces feelings of depression and anxiety, reduces the amygdala fear response and increases levels of self-confidence (Graeff et al., 1996). MDMA produces slight alterations in perception that facilitate imagination and memory (Harris et al., 2002), increased positive mood, increased feelings of closeness, greater compassion and increased empathy for oneself and others (Hysek et al., 2013). In common with 'classical' psychedelics, MDMA also acts at 5-HT_2 receptors, (Liechti and Vollenweider, 2001), which contributes further to the raised positive mood (van Wel et al., 2012). Increased dopamine and noradrenaline raise levels of arousal and awareness (Rothman et al., 2001), which can motivate a patient to engage in therapy and has been shown to promote fear extinction (Quirk and Mueller, 2008). And MDMA's effects at alpha-2 receptors, which contribute to the drug's effects on thermoregulation (Bexis and Docherty, 2005), may also contribute a paradoxical relaxation/sedation effect (Giovannitti et al., 2015), which could be beneficial in the context of trauma-induced hypervigilance. 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 (Thompson et al., 2007). However, this phenomenon remains debated (Kuypers et al., 2014). Other studies have shown oxytocin to dampen fear-related amygdala activity, causing a decrease in stress response and social anxiety (Kirsch et al., 2005; Domes et al., 2007).

The well-documented effects of MDMA used clinically give rise to its description as an 'empathogen' or 'entactogen' (Nichols, 1986). And taken together, these changes in social cognition, interpersonal closeness, and communication may influence the outcome of psychotherapeutic treatments for alcohol use disorder and comorbid psychological disorders (Jerome et al., 2013).

6. Will MDMA work for addictions?

Whilst the classical psychedelics (including LSD and psilocybin) have a rich history in the field of substance use disorders, MDMA has never been explored. Furthermore, the popular press is abundant with tens of thousands of anecdotal reports of how LSD and magic mushrooms, taken recreationally or in semi-therapeutic underground conditions, have helped drinkers to overcome their alcohol use disorder. However, there is a notable scarcity of anecdotal stories stating how 'ecstasy cured my alcoholism'.

Since the 1950s onwards, researchers have frequently shown how positive outcomes in substance use disorders with classical psychedelics are closely linked to the intensity of the induced mystical/spiritual effects of LSD or psilocybin, and similarly with ketamine; whereby the stronger the spiritual experience, the greater the maintained abstinence from substance use (Bogenschutz et al., 2015; Johnson et al., 2014; Krupitsky and Grinenko, 1997). Whilst there *is* also a mild subjective spiritual/mystical experience associated with MDMA use, this occurs in only 10–15% of first-time threshold dose users (Watson and Beck, 1991; Sumnall et al., 2006), as opposed to the 80–90% of mystical-type experiences reported by classical psychedelic use (Griffiths et al., 2006; MacLean et al., 2011).

However, MDMA Therapy has been shown to be an effective tool at tackling trauma, which is frequently described pre-morbidly by patients with alcohol use disorder (Stewart, 1996). The potential mechanistic action of MDMA's capacity for allowing users to better tolerate their worst memories has recently been demonstrated using fMRI (Carhart-Harris et al., 2013). And since the 1980s MDMA has been explored as a tool to treat underlying trauma (Greer, 1985), and associated reductions in substance use have also been observed (Greer and Tolbert 1986). More recently, MDMA-assisted psychotherapy for chronic, treatment-resistant PTSD has found statistically and clinically-significant gains (Mithoefer et al., 2010; Chabrol and Oehen, 2013) with results sustained at 3.5 years follow-up (Mithoefer et al., 2013).

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. In recent years mindfulness techniques, originally derived from *Vipassana* meditation, which encourage awareness and acceptance of thoughts, feelings and bodily sensations, have been increasingly explored as a potential approach for treating alcohol use disorder (Marcus and Zgierska, 2009; Hsu et al., 2008). Whilst mindfulness as a clinical tool remains formally untested as a therapeutic agent in combination with MDMA-assisted psychotherapy, clinicians in the field have commented on the parallels between the approaches, with Mithoefer et al. (2010) describing MDMA's capacity to "make yourself present in the moment", which is a core concept of mindfulness.

In respect of MDMA's lack of spiritual effects compared to classical psychedelics, MDMA is generally more easily tolerated than the classical psychedelics, with less perceptually disturbing effects compared to LSD and psilocybin. Not all patients are able to tolerate the classical psychedelic experience and compliance is a critical part of addiction therapy.

In summary, MDMA has the potential to enhance and intensify the psychotherapeutic processes in the treatment of alcohol use disorder. It may also address symptoms of other conditions that are frequently comorbid with substance use disorders, particularly those symptoms associated with a history of psychological trauma, and is well-tolerated.

7. Is MDMA therapy safe?

MDMA Therapy is not without its challenges. Some users of clinical MDMA experience an increase in anxiety associated with derealisation-type experiences (Mithoefer et al., 2010). Acute neurocognitive effects include a transient reduction in verbal and visual memory, which tend to resolve after the acute subjective psychological effects of the drug have worn off (Kuypers and Ramaekers, 2007). MDMA possesses only mild abuse potential. In the limited studies in which MDMA has been administered clinically in a therapeutic setting to healthy volunteers without any previous experience with ecstasy, subjects did not express a wish to use it outside of the clinical setting (Liechti and Vollenweider, 2001)

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and in the recent MDMA-PTSD studies carried out, illicit use of ecstasy after having used it clinically is very rarely observed (Mithoefer et al., 2013).

Acute MDMA produces increased blood pressure and heart rate and an increase in body temperature (Harris et al., 2002; Mas et al., 1999). Jaw tightness, bruxism, reduced appetite, poor concentration and impaired balance are also common (Mithoefer et al., 2010; Oehen et al., 2013). When the recreational drug ecstasy is taken outside of the clinical setting more serious adverse effects have been observed, including hyperthermia, liver disease and hyponatraemia (Rogers et al., 2009). But these are all features that can be easily controlled for in a clinical setting in which vulnerable patients can be screened, participants' vital signs are monitored throughout the MDMA session and follow-up sessions provide post-session support.

In the early-1990s specific concerns arose in the psychopharmacology community about potential MDMA neurotoxicity. Whilst some studies have demonstrated transient verbal memory deficits, slow processing speeds and a range of executive impairments, including spatial working memory (Hanson and Luciana, 2004) and verbal fluency impairments (Bhattachary and Powell, 2001) amongst recreational ecstasy users, other studies have reported a lack of such deficits (Back-Madruga et al., 2003; Gouzoulis-Mayfrank et al., 2003). Furthermore, contemporary studies have failed to show any significant long-term neurotoxicity associated with recreational ecstasy when controlled for use of other recreational drugs (Hanson and Luciana, 2010; Halpern et al., 2004), or have demonstrated that residual neurocognitive impairments are normalised after cessation of use of recreational ecstasy (Selvaraj et al., 2009). There have been no reports of long-term neurotoxicity or associated neurocognitive impairments when pure MDMA has been administered as part of a scientific study in a controlled clinical setting (Doblin et al., 2014; Mithoefer et al., 2013). It is important to stress, therefore that clinical MDMA is not the same as recreational ecstasy.

8. Conclusion: the future for MDMA science and therapy

As described, most contemporary MDMA Therapy studies have focused on PTSD. But the hypothesis behind the UK's first ever clinical MDMA Therapy study, the *Bristol-Imperial MDMA-for-Alcoholism (BIMA)* study, is that MDMA can be used as a safe and effective adjunct for psychotherapy in the treatment of alcohol use disorder. The study will recruit alcohol-dependent participants who have recently undergone a medical detox from alcohol. They will be enrolled in an 8-week course of supportive psychotherapy employing elements of Motivational Enhancement Therapy. As with all psychedelic-drug assisted psychotherapy courses, the majority of therapeutic sessions will be face-to-face non-drug-assisted sessions. But on two occasions participants will be administered open-label sessions of MDMA-assisted therapy, spaced two weeks apart. On each drug-assisted session participants will receive an initial dose of 125 mg MDMA, followed 2 h later by a 'booster dose' of 62.5 mg MDMA to prolong the experience. Throughout the drug-assisted session vital signs, including blood pressure and body temperature, will be monitored. Participants will remain in the treatment centre overnight after taking MDMA and mood and suicide risk will be monitored daily for a week. Participants will be 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 behaviours.

As the Multidisciplinary Association for Psychedelic Studies (MAPS) pushes ahead with Phase 3 studies in the USA for MDMA-Assisted Psychotherapy for treatment resistant PTSD we are seeing a broadening of the clinical possibilities for MDMA. MAPS envisages an FDA license for MDMA Therapy for PTSD by 2021, with an EMA European license by 2024 (MAPS, 2017). Meanwhile psychiatrists are increasingly recognising the role played by early psychological trauma in a range of mental disorders beyond that of only PTSD (Jeronimus et al., 2013). In the USA MDMA Therapy is being explored as a treatment for social anxiety associated with autism (http://www.mdma-autism.org/) and several UK teams have started planning an MDMA Therapy study for treating opiate use disorder (Morgan, 2017b).

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 public opinion must not be allowed to dictate the progress of medical research (Sessa and Nutt, 2007).

There remains much work to be done to convince a doubting medical profession and cautious governments that a compound that is experienced recreationally by 750,000 people every weekend in the UK may also, in its clinical form, have benefits for patients suffering with substance use disorders (Sessa, 2017b). Regulatory approvals associated with MDMA's status as a schedule one drug continue to hamper research; adding unnecessary costs that put research beyond the financial capabilities of many academic institutions and hold back progress (Sessa and Nutt, 2015).

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 treatment outcomes for alcohol use disorder that are little better now than they were 100 years ago. In this context, given the clinical burden, the lack of treatment efficacy and their continued distress, can we afford *not* to explore innovative options such as MDMA Therapy for treating our patients with alcohol use disorder?

Conflicts of interest

None.

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