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Cover picture


Dr Alexander ‘Sasha’ Shulgin (1925–2014), chemist, discovered and synthesised over 200 new psychoactive compounds. Recognising the limitations of animal studies, he tested these on himself and his friends; documenting the results in two books written with his wife Ann: Phenethylamines I Have Known and Loved and tryptamines I Have Known And Loved. He famously rediscovered the drug 3,4-methylenedioxy-N-methylamphetamine (MDMA) and introduced it to the psychotherapeutic community. MDMA’s 'empathogenic' therapeutic properties make it ideal for treating post-traumatic stress disorder (PTSD) and the UK’s first clinical study of MDMA for PTSD is now getting underway in the artist’s own words: The painting portrays Sasha holding an MDMA molecule that has a fiery warm glow and eagle's wings. Ann touches the molecule and gazes into the light. Around them radiate molecular symbols of Shulgin's many psychedelic discoveries.

Text by Ben Sessa.

We are always looking for interesting and visually appealing images for the cover of the journal and would welcome suggestions or pictures, which should be sent to Dr Allan Beveridge, British Journal of Psychiatry, 21 Prescot Street, London E1 8BB, UK or bjps@bja.ac.uk.
Can psychedelic compounds play a part in drug dependence therapy?

Ben Sessa and Matthew W. Johnson

Summary

After a 40-year hiatus there is now a re-viving of psychedelic drug therapy throughout psychiatry, with studies examining the use of psilocybin, ketamine, ibogaine and ayahuasca in the treatment of drug dependence. Limitations to these therapies are both clinical and legal, but the possibility of improving outcomes for patients with substance dependency imposes an obligation to research this area.

Declaration of interest

None.

The only real remedy I know for opium madness is ketumaria.

William James in *The Varieties of Religious Experience*

After one hundred years of modern psychiatry the treatments available for enduring remission from drug dependence for alcohol, opiates, stimulants and nicotine remain poor. Although pharmacological treatments exist they are associated with substantial failure rates. A wealth of studies explored psychedelic drug-assisted therapy in the 1950s and 1960s, but this research was curtailed prematurely in the wake of the 1960s recreational drug phenomenon. After a hiatus of several decades this research is now revisited with a number of contemporary studies examining the drugs psilocybin, ketamine, ibogaine and ayahuasca to directly tackle drug dependence.

Why concentrate on drug dependence?

People who are drug-dependent are often stigmatised, maligned by society and blamed. However, the experience of the authors – a child psychiatrist who now works in adult substance misuse (B.S.) and a behavioural psychologist who studies the environmental determinants of drug use (M.W.L.) – is that many of these patients are helpless, needy victims of adverse psychosocial circumstances. Their trajectory into drug dependence has been a journey from childhood trauma. Now they face not only their unresolved trauma but also the plight of drug dependence that ties them to a lifestyle of psychosocial and financial dysfunction. Because of the complexity of their aetiology and the psychological and physiological dependence that results, these disorders are very difficult to treat.

Alcohol addiction

One adult in 20 in the UK is a dependent drinker and one quarter of all adults drink in a hazardous fashion. Alcohol dependency and misuse is a major factor in offending behaviour. It is strongly related to crime, including domestic abuse, antisocial behaviour, public disorder, sexual assault and motoring offences. A meta-analysis of 361 controlled studies of treatments for alcohol dependence in 2002 identified 46 possible interventions. The brief intervention approach ranked highest and motivational enhancement ranked second. Pharmacotherapy with the gamma-aminobutyric acid (GABA) agonist acamprosate and the opiate antagonist naltrexone ranked third and fourth respectively. The lowest ranked approaches were designed to educate, confront, shock or foster insight regarding the nature of alcoholism. There remains a lack of coherence and agreement about the most efficacious alcohol dependence treatment. Meanwhile, taking into account alcohol-related health disorders and disease, crime and antisocial behaviour, accidents, loss of productivity in the workplace and domestic problems, the Department of Health estimates alcohol misuse is now costing around £20 billion a year in England alone.

Opiate dependence

Misuse of heroin and related opioids is a major public health concern, with over 123,000 people injecting heroin in the UK. Those who use heroin have a 12-fold increase in mortality relative to the general population and often present with severe physical, mental, social and criminal legal complications. Methadone and buprenorphine are the most commonly prescribed medications for opioid dependence. They have consistently been found to increase treatment retention and decrease opioid misuse, mortality, HIV risk and crime. However, these substitution treatments have limitations. Methadone is associated with medical risk and is contraindicated for some patients, and both medications are dangerous in combination with sedative drugs.

Stimulant dependence

Cocaine is the second most popularly used illegal drug in the UK. In its powder form it may be snorted or injected, and in its freebase form crack cocaine can be smoked and injected. There is no accepted substitution treatment for cocaine or other stimulants as there are for opiates. Treatments rather involve psychological strategies including contingency management, cognitive-behavioural therapy and motivational interviewing. Drug therapies are largely symptomatic (i.e. addressing comorbid depression, anxiety and insomnia) or treat coexisting opiate dependence.

Nicotine dependence

Although people who smoke are less marginalised than those using other drugs, tobacco is associated with more deaths than any other legal or illegal drug. The numbers are staggering –
tobacco kills over 1.2 million people annually in Europe alone. Although the most effective medications (varenicline, bupropion, nicotine replacement) improve success rates, the large majority of patients relapse even with these medications. There is a desperate need for improvement. An ongoing open-label pilot study in the laboratory of one author (M.W.I.) is showing promising results using psilocybin combined with cognitive-behavioural therapy for smoking cessation. If efficacy and safety are supported by a randomised trial, this approach may hold potential to have a substantial public health impact given the shocking mortality caused by smoking.

**Psychedelic therapy and substance misuse**

In the 1950s and 1960s psychiatrists Humphry Osmond and Abram Hoffer at the Weyburn Mental Hospital, Saskatchewan, Canada, used lysergic acid diethylamide (LSD) to provide a clinician-induced organic psychosis to encourage sobriety. They found that it was mystical spiritual experiences—not psychotic experiences—with the drugs that were associated with treatment success. With LSD they reported abstinence rates far surpassing other treatments before or since. Osmond, who famously coined the term ‘psychedelic,’ also administered LSD to Bill Wilson, the founder of Alcoholics Anonymous, who recognised LSD therapy as beneficial for alcohol dependence. A large number of studies to treat alcohol dependence with LSD psychotherapy were conducted by other researchers in the 1960s until psychedelic research collapsed for sociopolitical reasons in the wake of large-scale recreational drug use.

**Cross-cultural use of psychedelics**

There are examples of the naturalistic use of psychedelic plants to tackle addictions by indigenous populations: these include the West African use of the iboga root (containing ibogaine), the South American use of ayahuasca (containing dimethyltryptamine) and the North American use of the peyote cactus (containing mescaline); all of which have been reported to reduce rates of alcohol dependence.

**Possible therapeutic mechanisms**

Personality change is relevant to drug dependence, given that maladaptive personality traits often accompany drug use disorders. Two observational studies from the early 1960s suggested positive personality and other therapeutic changes in criminal offenders. With colleagues, M.W.I. has recently revisited prisoner personality change interventions with positive results. This idea of mystical-spiritual experience resulting in personality change was also explored recently in studies in which volunteers rated the psilocybin experience as having substantial personal meaning and spiritual significance. Subsequently sustained positive changes in attitudes and behaviour were consistent with changes reported by community observers. Another possible mechanism for the anti-addictive properties of hallucinogens may involve an ‘afterlow’ period of several weeks described in early clinical research. It was suggested that this period gave patients emotional strength to continue abstinence and experience decreased cravings. A recent paper by Bogenschutz & Pommy further explored potential psychological and biological therapeutic mechanisms of psychedelics in the treatment of substance misuse disorders.

**Contemporary studies**

A team in Russia in the 1990s, driven by the theory behind Osmond’s 1950s studies, investigated the potential role for psychedelic drug-assisted psychotherapy with ketamine for both alcohol and opiate addictions. The results of subsequent placebo-controlled studies on more than 1000 patients with alcoholism showed that ketamine produced total abstinence for more than a year in 66% of those in the ketamine group, compared with just 24% of the control group. Despite positive published results the Russian Federation forbids further research with ketamine. In addition to the previously mentioned study of psilocybin and nicotine addiction, an open-label pilot study investigating psilocybin-assisted psychotherapy in alcohol dependence is under way at the University of New Mexico (clinicaltrials.gov registration number NCT01534494). There are also observational studies in Mexico and New Zealand of ibogaine-assisted therapy and a study conducted in Canada looking at the role of ayahuasca in the treatment of drug dependence (see [http://maps.org](http://maps.org) for details of all these studies).

**Theoretical objections to psychedelic treatment**

There may be objections to treating drug dependence with other potentially misused drugs. However, current treatments for drug dependence already involve maintenance pharmacotherapy with controlled drugs. In seeking enduring remission, psychedelic drug-assisted psychotherapy is not simply maintenance therapy. Moreover, although psychedelic drugs can be misused, many of them (psilocybin, LSD) do not support compulsive drug-seeking.

**The psychedelic renaissance**

After a 40-year hiatus there is now a reversion of psychedelic drug therapy throughout psychiatry. Research teams at major academic institutions worldwide are investigating psychedelic drug-assisted therapy and several independent research groups have emerged to work collaboratively on the cohesive organisation of research. This research is still in its early stages and the most effective methods have yet to be evaluated. There are several limitations. For example, psychotherapy sessions that last for many hours would be expensive and are unlikely to be a first-line intervention. Moreover, some individuals would be excluded from psychedelic therapy for safety reasons. Another challenge is that many of these drugs are restricted at the Schedule I or Class A level, forbidding all medical use outside of highly regulated medical research. A medical future for these compounds would require a change in regulatory status (e.g. to the level at which compounds with accepted medical use such as morphine and amphetamine are regulated) and a plan for the manufacture of approved compounds.

Patients with drug dependence deserve the opportunity for the best available treatments from their psychiatric services. If there is a chance that psychedelic drug-assisted psychotherapy could improve outcomes for this population of patients, we owe it to them to research this area.

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Editorial

Making a medicine out of MDMA
Ben Sessa and David Nutt

Summary
From its first use 3,4-methylenedioxymethamphetamine (MDMA) has been recognised as a drug with therapeutic potential. Research on its clinical utility stopped when it entered the recreational drug scene but has slowly resurrected in the past decade. Currently there is enough evidence for MDMA to be removed from its Schedule 1 status of ‘no medical use’ and moved into Schedule 2 (alongside other misused but useful medicines such as heroin and amphetamine). Such a regulatory move would liberate its use as a medicine for patients experiencing severe mental illnesses such as treatment-resistant post-traumatic stress disorder.

Declaration of interest
None.

For those of us researching the development of 3,4-methylenedioxymethamphetamine (MDMA) therapy for patients with post-traumatic stress disorder (PTSD) the drug’s historical association with recreational ecstasy is a hindrance. Although clinical use precedes recreational ecstasy the media focuses primarily on the rare incidences of harm associated with misuses of the latter. After a quarter of a century of epidemiological evidence of MDMA’s low rates of morbidity and mortality (even when used recreationally as ecstasy), as well as mounting data supporting clinical MDMA as a therapeutic agent, we feel it is time to concentrate on the objective evidence-based research. Otherwise, we risk denying a population of needy patients a potentially important treatment. An important step towards recognising MDMA as a medicine is to move it from Schedule 1 to Schedule 2 of the UK’s drug classification system.

A brief history of MDMA in medicine
First synthesised in 1912 by the German pharmaceutical company Merck as a chemical precursor, MDMA failed to make an impact on the 1960s drug scene. In the 1970s a few psychotherapists were using it legally as a tool in couples therapy, where it was seen to help traumatised clients address repressed emotional memories without being overwhelmed by the negative affect that usually accompanies such memories. It was then banned in the mid-1980s in the wake of growing recreational use. No placebo-controlled studies were conducted with MDMA in the 1980s, but case-control studies showed MDMA could be used without adverse effects to produce qualitative improvements in psychological functioning and resolution of relationship difficulties.1

Controlled clinical trials
A recent placebo-controlled study of participants with treatment-resistant PTSD showed that 85% of those in the MDMA group (compared with 15% in the placebo group) no longer had a diagnosis of PTSD after three sessions of MDMA-assisted psychotherapy.2 These results were sustained at 3.5 years long-term follow-up, with no further MDMA interventions required and many patients reducing or stopping their regular psychiatric medications.3 A subsequent Swiss MDMA study demonstrated substantial improvements for treatment-resistant PTSD.4

How MDMA may work as an adjunct to psychotherapy
MDMA exerts its effects through 5-hydroxytryptamine (5-HT)1A, 5-HT1B, 5-HT2A, dopamine and alpha-2 receptors. It also produces oxytocin release, which improves bonding and raises levels of empathy. Its multiple and varied effects make the drug a good candidate for facilitating psychotherapy—especially for patients with post-traumatic symptoms, in which helping the patient to reach a position of empathic understanding and compassionate regard is part of their resolution and remittance of symptoms.5

Participants given MDMA are more likely to use words relating to friendship, support and intimacy, in comparison to the drug methamphetamine, which by contrast reduced participants’ discussions about compassion.6 MDMA appears to enhance the quality of social interactions and thereby improve relationships, recently tested using a simulated experimental paradigm of social exclusion by Frye et al, showing how participants taking MDMA exhibited reduced social exclusion phenomena.7 Similarly, MDMA enhances levels of shared empathy and prosocial behaviour compared with placebo.8 Furthermore, Wardle et al showed how MDMA can facilitate a faster detection of happy faces, and reduces the detection of negative facial expressions, which leads participants to view their social interaction partner as more caring.9 A recent study by Kirkpatrick et al comparing MDMA against intranasal oxytocin demonstrated the former produced greater improvements in prosocial communication.10

And the positive effects of MDMA appear consistent across different environments, with participants examined in San Francisco, Chicago and Basel demonstrating broadly similar prosocial outcomes.11

Recently, several groups have used neuroimaging to explore the actions of MDMA in the brain. For example, Carhart-Harris et al, using magnetic resonance imaging blood oxygen level-dependent and arterial spin labelling techniques, showed that MDMA reduced amygdala and hippocampus activity and selectively attenuated the magnitude of negative memories.12
Current restrictions around the use of MDMA in the UK

Given the evidence that MDMA is a useful and safe adjunct to the treatment of PTSD and has plausible mechanisms of action, one might well ask why MDMA is not available for clinical use. The answer is simple — when MDMA was banned in the 1980s it was put into Schedule 1 of the 1971 UN convention and in the UK placed in Schedule 1 of the Misuse of Drugs Regulations 2001. Both regulatory systems define Schedule 1 drugs as those with ‘very limited medical use’. This is no longer defensible. So what does being in Schedule 1 mean for researchers and doctors who wish to prescribe it? In most countries Schedule 1 drugs are subject to stringent controls. In the UK one needs a special license to hold or use a Schedule 1 drug, whereas Schedule 2 drugs, such as heroin and morphine, much more addictive and dangerous than MDMA, are available in all hospitals. Schedule 1 drugs cost about £5000, can take a year to obtain and require special criminal record checks, extra-secure pharmacy sales and police inspections. Only four hospitals in the country presently have them. Furthermore, production sites and distributors need the special license too, which massively escalates costs and limits the number of companies able to manufacture and supply clinical-grade material.

Safety and risks

One must distinguish the clinical use of pure MDMA from the recreational use of ecstasy. The former involves moderate, infrequent medically supervised doses whereas the latter often involves high dosage use, the risk of adulterants and the concomitant use of other drugs – especially cannabis, amphetamine and cocaine. There is no evidence that pure MDMA as proposed for therapy causes any lasting physiological or psychological harm. None of the controlled studies of MDMA-assisted therapy has demonstrated any significant neurophysiological impairments or evidence of dependence following its use clinically, validating the observed low risk of addiction when used recreationally. The fears about lasting neurophysiological damage, popularised in the 1990s, have since been challenged, further validating the epidemiological evidence of low rates of clinical problems associated with ecstasy use, despite its widespread popularity.

The concept of risk–benefit analysis is important when considering any medical interventions – pharmacological or otherwise. With dozens of individuals with post-combat treatment-resistant PTSD dying by suicide every day,15 the massive social, financial and clinical burden of untreated PTSD is far greater risk to society than the low risks associated with using MDMA in the clinical setting.

The future for MDMA research

Further Phase II MDMA-assisted psychotherapy for PTSD studies are happening, after which Phase III studies are planned across the globe. A planned functional magnetic resonance imaging study at Cardiff University will explore MDMA’s mechanism in individuals with post-combat PTSD to add more physiological data to the ongoing therapeutic studies. And an ongoing study underway in the USA is exploring MDMA’s ability to boost empathy and for adults with autism.

But for MDMA to become a medicine it needs to be removed from Schedule 1 and put alongside other therapeutic (but also misused) stimulants such as amphetamine and methamphetamine in Schedule 2. If the UK government advisory body on drugs, the Advisory Council on the Misuse of Drugs, recommends this to the Home Secretary, regulations can then be amended within weeks. It is important to note that the UK is not legally obliged to adopt the UN structure for scheduling drugs and based on medical advice put heroin in Schedule 2 against the UN recommendation. Similarly, in another example the UN placed tetrahydrocannabinol in Schedule 1 in 1971, but in the UK it is available (in the form of the drug sativa) and placed in Schedule 4. Moreover there is no reason to suppose putting MDMA into Schedule 2 would have any impact on illicit use of ecstasy, just as pharmaceutical heroin in Schedule 2 is almost never diverted into criminal hands.

We call on the Advisory Council on the Misuse of Drugs to recommend MDMA become a Schedule 2 drug. This will allow medical research to explore the full potential of MDMA as a medicine for treatment-resistant PTSD and other possible brain disorders.

Conclusion

MDMA has been subjected to inappropriate, non-evidence-based, legislative restrictions. These have not effectively reduced the harm or burden of recreational ecstasy use on society but they have effectively held back research on clinical MDMA. We urge the regulatory authorities to consider whether a move from Schedule 1 to Schedule 2 might more accurately reflect MDMA’s relative harms and safety, while also facilitating greater research of the substance for possible therapeutic uses within psychiatry.

Acknowledgements

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Léon Bonvin
Raymond Cavanaugh Jr

Born in the outskirts of Paris in 1834, Léon Bonvin was the son of a policeman and a seamstress. There were numerous siblings from multiple marriages, and money was scarce. Léon’s strongest bond was with his older brother François. They shared a desire to draw and a precocious aesthetic sensibility. Apprenticed to a printer in his adolescence, François would give the younger Léon artistic advice for the remainder of his life.

Most of Léon’s earliest works were charcoal renderings of his austere surroundings. He would later work in graphite, pen and ink, and eventually in the watercolour medium, with which he would carve his niche. Oil painting was a rare activity for him, because he was rarely able to afford oil paints.

Though lacking in materials, Bonvin benefited from his elder brother’s guidance. François suggested that he study the Dutch masters and pay particular attention to their meticulous realism and use of outline. In time, the younger brother would employ sepia-toned ink outlines to produce his own meticulous realism in the form of watercolours with starting, quasi-photographic effects.

However, this stylistic innovation did little to enhance Bonvin’s overall quality of life. Forced to work tirelessly at his job as inkeeper, there was precious little time for the artistic vocation. Early morning and sunset were usually the only times at which he could perfect his coloured magic.

The online art publication The Blue Lantern explores the psychodynamic elements of Bonvin’s Interior of a House with an Open Door. This painting has a very claustrophobic feel, which likely reflects his painter’s ongoing sentiments of frustration and confinement. Though the painting, through its “open door”, includes a “glance of a wider world”, this glance is “obscured by blazing sunlight”.

The early 1860s saw Bonvin marry, start a family, and sink further into poverty. By January 1866 his financial situation had become dire. Carrying as many paintings as he could, he headed to Paris and approached an art dealer: “Too dark,” was the dealer’s response. Having been dismissed with those few words, the starving artist was sent on his way, not one franc richer. Emotionally drained, Bonvin went to a hill that overlooked the plains of Icy. This view had inspired some of his most passionately painted watercolours.

Here, hours later, the painter was found hanging from a tree. If there was any good to come of this demise, it was that a posthumous charity auction of his works raised enough money to spare his family from utter destitution.