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EDITORIAL

Should addiction researchers be interested in psychedelic science?

As recently noted by Strauss, Bright and Williams [1], while much of the Western world has been experiencing a renaissance in research into 'psychedelic science' over the past decade [2], there has been no such research conducted in Australia. In Europe and the USA, studies have been conducted into lysergic acid diethylamide (LSD) that have improved our understanding of brain function [3] and reduced existential anxiety associated with dying [4], while psilocybin-assisted psychotherapy has shown promise as an intervention for treatment of refractory depression [5]. Psilocybin-assisted therapy has also been shown to reduce depression and anxiety among people with end-stage cancer [6], with two recent randomised controlled trials (RCT) showing significant improvements in quality of life [7,8]. In collaboration with the researchers involved in this research, the Heffter Institute is in discussions with the US Food and Drug Administration (FDA) about commencing Phase III multisite trials. Meanwhile, 3,4-methylenedioxymethamphetamine (MDMA) is proving efficacious as an adjunct to psychotherapy in the treatment of post-traumatic stress disorder (PTSD) [9–12]. This new research is occurring at prestigious institutions such as New York University, University of California, Los Angeles, Johns Hopkins University and Imperial College London, following a 30 year embargo on psychedelic research that commenced when President Nixon declared his 'War on Drugs'.

We believe that addiction researchers worldwide should be interested in these developments, for several reasons. First, there are indications that psychedelic-assisted therapies might be effective in improving success rates in the treatment of substance use disorders. It is hypothesised that the mechanism of action might involve mystical states that have been shown to be reliably produced in an RCT of psilocybin [13]; the personal significance of these effects was maintained at 14 month follow up [14], including positive changes in personality [15]. The neurological basis of these effects is proposed to be a reduction of blood flow in the default mode network [3]. In an open-label trial of 15 people examining psilocybin-assisted psychotherapy for the treatment of tobacco addiction, 80% of participants remained abstinent at 6 month follow up [16]. In contrast, an RCT of varenicline [17], the most efficacious pharmacotherapy for smoking cessation [18], found that only 25.5% of participants were abstinent at 12 months. This team at Johns Hopkins University has just published the results of a survey of 358 people who reported that psychedelic drugs had helped them quit smoking and 74% had abstained for more than 2 years [19]. Consequently, this team is initiating an RCT of psilocybin-assisted psychotherapy for smoking cessation involving 40 participants [20]. Meanwhile, a proof-of-concept study has found that treatment of alcohol dependence with psilocybin-assisted psychotherapy yielded similarly impressive effects [21]. This team at New York University is now undertaking an RCT of 180 people that includes functional magnetic resonance imaging scanning [22].

Second, while it is not considered a prototypical psychedelic, new research is showing that MDMA holds great promise in curing treatment-refractory PTSD [9]. This is significant because many people who develop substance use disorders have a history of psychological trauma [23,24]. Within the Australian Treatment Outcomes Study, 41% of people receiving treatment for heroin dependence met criteria for PTSD [25]. Some have suggested that the rates of trauma among people with substance use disorders may be even higher than first thought. Among a sample of 423 Dutch people with a range of substance use disorders, Gielen *et al.* [26] found 46.2% whose primary drug of choice was alcohol met the criteria for PTSD.

MDMA was used in psychotherapy in the 1970s and early 1980s as a safe adjunct to couples counselling and to address psychological trauma, prior to its emerging popularity as a recreational drug. The first clinical study reporting on the therapeutic effects of MDMA was published in 1986 by Greer and Tolbert [27]. Described accurately as an 'empathogen' or 'entactogen', the compound has the unique properties of establishing empathy with clinical staff while concurrently creating an emotional openness in the client that allows him or her to reprocess the traumatic event/s within the window of tolerance, without fear or shame [9]. MDMA appears to function as a catalyst for the psychotherapeutic process and is described by Sessa

as 'psychiatry's antibiotic' [28]. Unlike many other drugs used in the context of psychiatric illness, MDMA acts to facilitate psychotherapy, using low doses on only several occasions in a controlled, supportive environment by appropriately trained therapists, making adverse outcomes very unlikely.

The renaissance in psychedelic psychotherapy has been gathering pace since 2001. Following the closure of a Spanish trial due to political pressure in 2000, the first completed RCT looking at the efficacy of MDMA-assisted psychotherapy for treatment-resistant PTSD found that after 12 sessions, 86% of participants no longer met DSM-IV criteria for PTSD [15]. The treatment involved a preparation session, then two MDMA sessions separated by a few weeks with integrative sessions after each MDMA session. The effects were maintained at a 3.5 year follow up, with only 10% of participants relapsing [16].

Further Phase II trials have been completed in Switzerland [12], South Carolina, Colorado, Canada and Israel. Armed with accumulating positive results, trial sponsor, the Multidisciplinary Association for Psychedelic Studies (MAPS) has been granted permission by the US FDA to progress to a Phase III trial, potentially under the breakthrough treatment designation. Because of the large effect size of the pooled data, with two-thirds of participants no longer meeting the criteria for PTSD, the FDA approved a smaller sample size than typically would be required for a Phase III, study and there is the potential for people to access MDMA-assisted therapy in the USA through a compassionate use scheme [29].

Psychedelic Research in Science & Medicine (PRISM) was incorporated in 2011 with the support of MAPS to initiate a Phase II trial of MDMA-assisted therapy among Australian war veterans. A government report found that 292 soldiers died from suicide between 2001 and 2014, with most deaths occurring among ex-service personal, leading to a Federal Senate enquiry that is currently underway [30]. Many of these deaths could be attributed to PTSD and many more Australian soldiers are dying from suicide than have died in recent conflicts. As such, it was believed that this study would be widely supported; however, PRISM has faced a number of barriers, including a veto of the proposed study by the Deputy Vice Chancellor (Research) of a Victorian university before the application even reached its Human Research Ethics Committee. PRISM believes that it is essential that the clinical use of MDMA be differentiated from the recreational use of ecstasy [1,31]. Most negative research regarding the safety of MDMA have been derived from animal studies in which extraordinarily high doses are administered [32], or in epidemiological research of the recreational use of ecstasy that may or may not contain MDMA, and in which a number of confounding factors limit the interpretation of the results [31]. Notably, the MAPS research has demonstrated the very low abuse potential of MDMA when administered in a clinical context: Of 107 participants in their Phase II trials to date, only one has attempted to replicate the therapeutic benefits of the MDMA-assisted therapy through personal experimentation [11]. The self-medication proved ineffective and was not repeated.

For some time, the treatment of PTSD was contraindicated if a person had a substance use disorder [33], yet the treatment of the substance use disorder alone would likely exacerbate the symptoms of the person's PTSD. The development of interventions such as concurrent treatment of PTSD and Substance Use Disorders Using Prolonged Exposure has provided an evidence-based treatment for people with substance use disorders who have comorbid PTSD [34,35]. Such integrative treatment makes intuitive sense given the inextricable interaction between both conditions.

Sessa [36] has proposed a proof of concept study in the UK that aims to provide an alternative treatment for people with a substance use disorder who have a history of psychological trauma. This treatment will integrate motivational interviewing with MDMA-assisted psychotherapy and will provide an opportunity to explore the possibilities of MDMA in the treatment of substance use disorders. The addictions field should be watching with interest as the outcome of this work could be paradigm-changing, because MDMA appears to both enhance and accelerate the psychotherapeutic process. With evidence supporting the benefits of psychedelic-enhanced psychotherapies accumulating exponentially, addiction researchers should consider the implications of the recent renaissance in psychedelic science.

Conflicts of interest

Dr Stephen Bright and Dr Martin Williams are board members of PRISM, a not-for-profit registered charity that aims to assist researchers initiate and fund psychedelic research in Australia. Dr David Caldicott has no conflict of interest to declare.

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