Psychedelics and related drugs: therapeutic possibilities, mechanisms and regulation

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"Psychedelic substances, if they are used in proper ways, are very helpful for mankind." Albert Hoffmann

The word 'psychedelic' derives from the Greek terms for mind – psyche – and 'delos' which means 'clear, manifest' so in essence psychedelic drugs can be seen as the prototype 'window on the mind' concept. The term was originally coined in the 1950s to describe lysergic acid diethylamide (LSD), mescaline and other hallucinogens, drugs that profoundly alter human experience. These have subsequently been show to act primarily as agonists at the 5-HT_{2A} receptor in the brain. Research into the therapeutic potential and mechanisms of action of psychedelic and related drugs peaked in the late 1960's but then stagnated for 50 years after the 1971 UN Psychotropics Convention made psychedelic research with humans almost impossible to carry out (Kyzar et al, 2017).

Recently however, this area is experiencing a renaissance as drugs often associated with recreational use – such as LSD, ketamine and cannabis/cannabinoids – have been shown to have therapeutic potential in a range of disorders such as treatment-resistant depression, suicidal ideation and some paediatric epilepsies. Further, recent pilot studies suggest that MDMA as well as the classic psychedelics, LSD and psilocybin, may contribute to the pharmacopeia for post-traumatic stress disorder (PTSD) and other difficult to treat psychiatric disorders. Research has also been stimulated by functional neuroimaging studies of single doses of psychedelics showing that they produce widespread changes in brain connectivity as well as profound alterations to perception and cognition. At the same time, as one would expect from a relatively fledgling area, many questions remain about mechanisms of action, safety and efficacy. These include what type of psychological therapies best combine with which type of psychedelic drug, whether some types of drug have benefits even without psychological treatment, what the optimal doses are, from single dose through to intermittent or repeated dosing. The current renaissance in empirical psychedelic research stimulated this Special Issue of Psychopharmacology. The articles are grouped into three

sections: Clinical efficacy and clinical issues; Effects and Mechanisms of action; Regulation and history.

Clinical efficacy and clinical issues

Four studies address the promising new therapeutic potential of MDMA, ketamine, LSD and cannabis for conditions ranging from PTSD to treatment-resistant depression (TRD). Building on recent pilot studies supporting a therapeutic potential of MDMA as an adjunct to psychotherapy in post-traumatic stress disorder PTSD, Pitts and colleagues review the preclinical and clinical evidence concerning the individual S(+) and R(-) enantiomers that comprise (+) MDMA. They conclude that R(-)-MDMA may have a better side-effect profile than S(+), and that future studies should directly compare the potential therapeutic advantages of both enantiomers in humans. Another drug, ketamine, administered intravenously (iv), intramuscularly (im) or intra-nasally (in), has been used with great success as a rapid-onset treatment for TRD and associated conditions. de Gioannis et al conducted a retrospective review of clinical records of patients receiving long-term oral ketamine as an adjunctive treatment of PTSD and TRD, and concluded that long-term oral administration is also a viable option. Psilocybin shows promise in the treatment of TRD. Robin Carhart-Harris et al report a 1-week to 6 months follow up of TRD patients who were given two separate single doses of psilocybin with psychological support as part of an earlier open-label pilot study. The investigators report that marked symptom improvements observed at 5 weeks post-treatment were still significant at 6 months, suggesting a full double-blind trial would be warranted. Finally, cannabinoids have been proposed for a range of conditions. Yet, concerns have been raised about the potential for misuse or problematic use, addressed here in a large study conducted in Canada by Martel et al. After baseline measures, 265 patients were initiated onto cannabinoid treatment and were re-assessed every 3 months for a year. Most patients showed no problematic use and the roughly 25% who did were more likely to have had a past-year history of substance misuse and previous psychiatric problems. Martel et al thoughtfully discuss the clinical and policy implications of these findings for cannabinoid treatments.

Mechanisms of action and effects

Nine articles focus on the effects of psychedelic and the mechanisms underpinning these.

Retrieval of a memory can return it to a plastic, malleable state, which may provide an opportunity to 'rewrite' aberrant, unwanted memories. For example, a hallmark symptom of PTSD are involuntary memory intrusions that are related to the trauma experience. Or again, substance use disorders (SUDs) are associated with maladaptive memories which can direct the individual's attention to drug-related rather than natural rewards in the environment. Fattore et al's thoughtful review focuses on one process for changing labile memories via reconsolidation. They review the effects of ketamine and cannabinoids on both traumatic and appetitive maladaptive memories and suggest that both drugs act on a process termed 'metaplasticity'. They argue that the ability to change such memories offers a novel intervention for PTSD and SUD.

Hudson and colleagues review both preclinical and clinical evidence on the influence of different phytocannabinoids on emotional memory processing (EMP). They conclude that the mechanisms underpinning these effects are the actions of cannabinoids within the ventral hippocampus and associated corticolimbic structures which modulate EMP via changes in mesolimbic dopamine activity, salience attribution and signal transduction pathways.

Two empirical studies then directly address issues of how the effects of psychedelics may be mediated by changes in emotional processing. Using a sensitive dynamic facial emotion recognition task, Stroud et al. assessed individuals with TRD before and after two separate doses of psilocybin and compared them with healthy controls at similar time points. Psilocybin improved the speed of recognising facial emotions in the depressed group so that they were as fast as controls after treatment, and this speed increase correlated with a reduction in anhedonia over the same time period. Dolder, Liechti and colleagues used a facial emotion recognition task (FERT) to compare the effects of three stimulants (MDMA, methylphenidate and modafinil). They found that MDMA was the only one of the three drugs which impaired fear recognition and increased mislabelling of emotions as happy. Whereas all three drugs produced similar hemodynamic and adverse effects, MDMA had distinct subjective, emotional, sexual and endocrine effects from other two drugs.

Kim Kuypers and colleagues report how the 5-HT2A receptor antagonist, ketanserin affects responses to a single dose of MDMA on responses to emotional sounds and biases towards emotional and social stimuli. MDMA reduced the arousal induced by negative sounds and ketanserin blocked this effect, extending previous findings using only visual emotional stimuli.

Tomas Palenicek et al investigated the effects of a single dose of psilocybin on auditory event-related potentials (ERPs) and mismatch negativity (MMN). Pre-attentive cognition (MMN) was unaffected whilst processing in the early perceptual level (N100) and in higher-order cognition (P300) was significantly disrupted by psilocybin. They draw out implications of these findings for the role of 5-HT2A receptors in disrupted information processing

Kaelen et al take a mixed qualitative/quantitative approach to exploring the potential role of music in psychedelic therapy. They qualitatively assessed interviews with individuals diagnosed with TRD who had taken part in a pilot study of psilocybin as an adjunct to psychotherapy, which included music. They report that the nature of the experience of music was associated with reductions in depressed mood 7 days after the drug.

Dose-response studies of psychedelic effects in humans are still rare. In a timely addition, Theresa Carbonaro and her colleagues report a study which compares 3 separate doses of psilocybin with dextromethorphan (DXM). Both drugs produced similar physiological effects and similar psychomotor impairments. In contrast, psilocybin produced relatively greater visual, mystical-type, insightful, and musical experiences whereas DXM producing greater disembodiment.

There are many anecdotal reports that psychedelic experiences induce profound changes in consciousness and insight . Schmid et al explored this by assessing mystical-like experiences, well-being and personality at three time points: before and 1 and 12 months after one dose of LSD was administered in a controlled laboratory setting. Ten of the 14 participants reported positive, long lasting subjective effects of LSD 12months after the experience, rating LSD in the top 10 most meaningful experiences of their lives. In a brief commentary, Carhart-Harris et al suggest that psychedelic drugs may exert therapeutic effects via inducing a sense of ‘connectedness’ and suggests ways this might be tested empirically.

Regulation and histories

A commentary by the psychiatrist Ben Sessa describes a 'psychedelic renaissance' involving both classic psychedelics such as LSD and psilocybin but also the entactogen MDMA. Although he describes "heroic steps forward", he sees these taking place slowly "on the back of an elephant" rather than with the speed of a space rocket and outlines various regulatory and societal impediments which need to be overcome before carrying out research with psychedelics. The Multidisciplinary Association for Psychedelic Studies (MAPS) have a long history of supporting this area of research and Feduccia et al describe how MAPS have developed their particular program on MDMA-assisted psychotherapy for PTSD. Positive results of recent Phase 2 trials provide the rationale for Phase 3 multi-site trials that are due to begin in 2018.

A timely review of the abuse potential of kratom is provided by Jack Henningfield and colleagues. Kratom, a plant of the species *Mitragyna speciosa*, has a long history of use in for pain conditions and in the last century for assisting opiate withdrawal. Currently there is controversy about whether the US Drug Enforcement Administration (DEA) and Food and Drug Administration (FDA) should put it in Schedule 1 of the Controlled Substance Act (CSA). Henningfield et al examine kratom in light of the 8 factors required by the CSA to determine abuse potential. They conclude that some form of scheduling may be warranted but placing kratom in Schedule 1 would effectively ban it and create both public health problems for users and barriers for future research.

The regulatory history of research on LSD in the US from 1949 to 1987 is the topic of the last paper in this Special Issue. Bronson describes how regulations changed over the years about scientific standards of clinical drug research, standards which many of the 1960s LSD studies struggled to meet. She concludes that these early studies should be viewed as providing pilot data on safety and efficacy and at best, generating hypotheses that could be tested under modern scientific and regulatory standards.

Overall, the articles in this Special Issue illustrate the breadth and diversity of research on psychedelic drugs, and how, in terms of high scientific quality, the area is now experiencing a *naissance* more than a *renaissance*. Regulatory changes that facilitate rather than obstruct research with these compounds will significantly aid progress in this field.