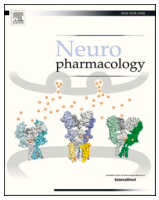
Neuropharmacology 236 (2023) 109610

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm



Psychedelics: Threshold of a Therapeutic Revolution

A B S T R A C T

This Special Issue of Neuropharmacology on psychedelics provides a timely and comprehensive update on progress following the previous Neuropharmacology Special Issue "Psychedelics: New Doors, Altered Perceptions". Remarkable advances have been made in basic and clinical research on psychedelics in the five years since 2018.

It is partly based on the seminar series focused on psilocybin organized by the National Institutes of Health (NIH), USA from April to June 2021, the "NIH Psilocybin Research Speaker Series". Participants were world leading experts, including scientists, medical practitioners, clinical psychologists and oncologists, and attendees from additional disciplines of patient advocacy, law, government science policy and regulatory policy. To provide a global perspective, their contributions are complemented with reviews by some of the world's most eminent scientists in the field.

The US Food and Drug Administration (FDA) has granted two breakthrough therapy designations for psilocybin in treatment resistant depression (TRD) in 2018 and major depressive disorder (MDD) in 2019, as well as for MDMA for the treatment of post-traumatic stress disorder (PTSD) in 2017. Clinical trials are in progress to assess the therapeutic value of psilocybin in MDD and TRD, and in other indications such as cancer-related anxiety and depression, anorexia, PTSD, substance use disorders and various types of chronic pain.

The contributors' insights should assist basic and applied science for transition of psychedelics from bench to potential mainstream therapies. The implications are global, because FDA approval of these new medicines will increase international interest and efforts.

1. Guest Editors' Preface to "Psychedelics: Threshold of a Therapeutic Revolution"

This 2023 Special Issue of Neuropharmacology on Psychedelics provides a timely and comprehensive update on progress in the 5 years since the previous Special Issue (Psychedelics: New Doors, Altered Perceptions) was published by Neuropharmacology. It would not be overstating the case to say that remarkable progress has been achieved in basic and clinical research on psychedelic drugs in the period since 2018.

This new Special Issue is largely based on a seminar series on psychedelic substances with a focus on psilocybin that was organized by the National Institutes of Health (NIH) in the USA from April 22nd to June 10th, 2021, the "NIH Psilocybin Research Speaker Series" (see accompanying Editorial by Xi et al. (2023). Participating in the event were world leading experts in the area, including scientists, medical practitioners, clinical psychologists and oncologists. There were also attendees from additional disciplines in this rapidly growing field of research, including those representing patient advocacy, law, government science policy and regulatory policy.

This Special Issue came about following an expression of interest by the NIH Speaker Series program panel to publish papers based on the lectures, appropriately updated for the journal. To provide a global perspective on the status of psychedelic research and development, contributions from the NIH Speaker Series have been complemented by invited reviews written by some of the world's most eminent scientists in the field.

To date, the USA Food and Drug Administration (FDA) has granted two breakthrough therapy designations for psilocybin, one for treatment resistant depression (TRD) in 2018, and a second for major depressive disorder (MDD) in 2019, as well as for MDMA for the treatment of post-traumatic stress disorder (PTSD) in 2017. Clinical trials are in progress to assess the therapeutic value of psilocybin not only in MDD and TRD, but also in other indications such as cancer-related anxiety and depression, anorexia, PTSD, substance use disorders and various types of chronic pain.

The new knowledge contained in the collection of expert reviews in the Special Issue is intended to provide a clear and critical appraisal of the advances and challenges for psychedelic drug development. The contributors' insights are designed to assist basic and applied science for the transition of psychedelic drugs from the bench to potential mainstream therapies based on the strategies that are likely to be initially subjected to evaluation in the USA. The implications are global because the FDA approval of new, psychedelic-based medicines will inevitably increase international interest and efforts.

The reviews in this Special Issue are divided into sections comprising firstly Policy, Ethics and Legal Issues, Regulatory Aspects of Drug Development, Basic Research, Clinical Research, and Therapeutic Applications.

2. Policy, Ethics and Legal Issues

The section commences with a review by Belouin et al. (2022) on the raft of policy considerations that need to be addressed to enable

https://doi.org/10.1016/j.neuropharm.2023.109610

Available online 27 May 2023

equitable access to psychedelic medicines should they become available to patients. Psilocybin and MDMA may receive full FDA approval within a few years with similar regulatory submissions concurrently being considered in several other countries. The authors discuss safe and ethical uses of psychedelics with regard to standards of practice, consumer protection, development of data standards, safeguarding access, and community education in anticipation of potential FDA decisions on the use of psychedelic drugs as essential contributors to innovative mental health therapies. Given the complexity of the issues, the authors discuss how a "real world" harm-reduction framework could be co-created through a government sponsored public-private partnership where the stakeholders would engage to develop and disseminate best practices and policies to advance and protect public health.

The safe use of psilocybin-facilitated psychotherapy in vulnerable populations is considered by Ortiz et al. (2022). Vulnerable populations bear a disproportionate mental health burden but have been largely neglected in the clinical psilocybin literature. The authors address these concerns by detailing the challenges and opportunities to evaluate psilocybin-facilitated psychotherapy in such populations, including recruitment strategies, appropriate communication and assessment of subjective effects, building therapeutic alliance, multicultural competence and flexible study designs.

New ethical and policy issues that need to be employed for the use of psychedelics in psychiatric indications are critically discussed by Smith and Appelbaum (2022). The use of classical psychedelics as licensed pharmaceuticals raises numerous ethical and policy challenges with respect to the current limitations of the evidence-base on the use of these powerful pharmacological compounds. These issues are influenced by the psychoactive properties of psychedelics, previous use in unregulated settings, rapid commercialisation, and the means and speed at which they are transitioning from Schedule 1 controlled drugs in the USA to legalised use.

Psilocybin is the most researched of the classical psychedelics and also the most advanced in terms of progress through the FDA's clinical development and drug approval process. Marks (2022) outlines and critically discusses the legal complexities that will accompany the US roll-out of psilocybin as a medically licenced pharmaceutical. It covers the state and local legislation of psychedelics in 5 broad categories: decriminalisation, supported adult use, medical use, clinical research, and policy analysis.

Sensationalism, exaggeration, and misinformation about the use of psychedelics in social and mainstream media is a fact of life. Sellers and Romach (2023) have written an excoriating review detailing the frequently misleading briefings given by drug developers and social media platforms which exaggerate the benefits and underplay the problems that psychedelics have encountered in clinical development. The authors also postulate that it might be feasible to circumvent many of the scientific, clinical and regulatory challenges associated with using high doses of psychedelics by low-dose or micro-dose treatment regimens. Moreover, these treatment options would be logistically simpler and more cost-effective than the high-dose/intensive psychotherapy model thereby increasing the availability of psychedelic therapies to all individuals who require treatment.

3. Drug Discovery and Development

Psychedelic compounds from natural sources have been employed in traditional healing practices for centuries and their transition into mainstream pharmaceutical development has provided an expedited route to drug approval and marketing. For example, the FDA has determined that some classical psychedelic substances (e.g., LSD, psilocybin and MDMA), which have been extensively evaluated through animal experiments, clinical experience, and epidemiological studies, may obviate the need for performing new, dedicated, abuse-related studies (Calderon et al., 2022). Nonetheless, there are well established safety concerns associated with the classical psychedelics and they will need to be addressed when developing the next generation of novel psychedelics for medical use. David Heal et al. (2022) discuss non-clinical experimental approaches to detect the psychedelic properties of novel compounds and predict their efficacy in clinical trials. They describe screening procedures to assess the safety and toxicity risks that these drug-candidates may pose to humans during clinical development and later as marketed drugs together with assessing their potential for misuse and abuse.

This is complemented by the review on considerations in the evaluation of abuse potential of classical psychedelics during drug development by Calderon et al. (2022). These psychedelic compounds were placed in Schedule I when the US Controlled Substances Act (CSA) was introduced in 1970, because they were assumed to have high abuse potential and had no established therapeutic use (Henningfield et al., 2022). The review by Calderon et al. (2022) details the experimental information that will be needed to support a recommendation for rescheduling of these psychedelic substances to lower drug schedules should any of them receive FDA approval.

Jack Henningfield assembled a group of eminent scientific researchers, clinicians, and drug developers from leading academic institutions, National Institutes of Health (NIH), and Substance Abuse and Mental Health Services Administration (SAMSHA) to provide a holistic assessment of abuse potential of psychedelic substances when considering submission of New Drug Applications (NDAs) and implications for CSA Scheduling by the FDA (Henningfield et al., 2022). The authors also critically assess the implications of the CSA for research and pharmaceutical development, the path to approval of psychedelic medicines, and their subsequent rescheduling from Schedule I controlled drug status in the US. Human abuse potential studies typically employed in central nervous system (CNS) drug development may be problematic for novel psychedelic drug-candidates with powerful hallucinogenic effects, and alternative strategies are described.

4. Basic Research

Wulff et al. (2023) have reviewed the preclinical models and experimental approaches used to explore the potential neurobiological actions of psychedelic drugs. The findings offer insights into potential mechanisms underpinning their immediate pharmacological effects including receptor targets and activation of various downstream signalling cascades. They hypothesize on the biological processes responsible for the long-lasting amelioration of symptoms induced by the psychedelics. Potential mediators include changes in synaptic structure and function, network connectivity, gene expression and suppression of inflammation. An improved mechanistic understanding of psychedelic drug actions will help in their development for various therapeutic indications.

Given that serotonin is generally considered to produce pro-inflammatory effects, the highly potent anti-inflammatory properties of certain psychedelic molecules is one of nature's great enigmas. Charles Nichols (2022) describes the initial discovery by his research group that specific psychedelics are potent anti-inflammatory agents and immunomodulators in peripheral tissues. The author proposes that these psychedelic molecules represent a new class of anti-inflammatory compounds that will be steroid-sparing and effective at sub-behavioural levels with potential to treat a variety of inflammatory diseases.

Mescaline derived from the peyote cactus has been used in traditional ceremonies for more than 5000 years. Although mescaline is one of the oldest known hallucinogens, it is a relatively under-researched and neglected psychedelic. Vamvakopolou et al. (2022) address this gap with a review of findings from preclinical and clinical research describing mescaline's pharmacology, and behavioural and psychotropic effects.

5. Clinical Research

Psychedelic drugs may herald a revolution in the way that pharmacotherapy is employed in psychiatry and various non-psychiatric indications. The fact that naturally occurring psychedelics have been imbibed by humans for millennia and extensively researched in laboratories has created the illusory belief that we understand everything that is important about these compounds, whereas in reality, we don't. David Nutt and his colleagues (2022) assess psychedelic drugs as therapeutic agents in terms of current knowledge and future directions for research. Accumulating evidence of transdiagnostic efficacy is eliciting a re-think of current diagnostic and symptom-specific approaches to psychiatry. The authors sound a cautionary note about the consequential, large-scale investment in this area and expansion of pharmaceutical companies. They stress the need for additional reliable research to define the neuro-biological effects of classical psychedelics and the development of an improved, new generation of psychedelic drugs.

Although there is currently no broad agreement on the brain mechanisms underpinning the complex effects of psychedelics, hypotheses have mainly focused on the actions of these drugs to reset neuronal connections in higher brain areas. Aquil and Roseman (2022) have taken a different approach and discuss the importance of sensory dimensions in psychedelic brain dynamics, experience and therapeutics. The authors present evidence from neuroimaging, pharmacology and clinical psychology studies where sensory alterations induced by psychedelics play a key role in determining psychedelic experience and therapeutic outcomes and are not merely "epiphenomenal by-products".

Every collection of review articles needs at least one thought-provoking and revolutionary idea to propel progress in the field. Robin Carhart-Harris et al. (2022) have stepped-up with a highly innovative hypothesis on canalization, plasticity in psychopathology, and the therapeutic mechanism of psychedelics. The authors differentiate between two types of plasticity, an early one, 'TEMP' for Temperature or Entropy Mediated Plasticity and 'canalization' (referring to phenotypic stabilisation). In this article, they propose that 'pathological' phenotypes develop by mechanisms of canalization as responses to adversity and associated distress or dysphoria. They propose that TEMP plus psychological support can oppose entrenched canalization.

6. Therapeutic Applications

Zia et al. (2023) discuss the early-stage research to determine whether psychedelics may hold benefit in the treatment of chronic pain conditions. Chronic pain is debilitating and blights the lives of a substantial proportion of the population. Moreover, it is often unresponsive to analgesic and non-steroidal anti-inflammatory drugs. The authors' proposal is a more holistic approach to the management of chronic pain should be adopted including biopsychosocial interventions to treat emotional, psychological and functional components of the condition. Strategies include key areas of research required to answer the question whether psychedelic compounds have sufficient benefit in chronic pain to gain approval by regulatory authorities.

In their commentary, Schindler (2022) summarize the evidence on the therapeutic effects of psychedelic drugs in treating headache and chronic pain disorders. Attention is focused on preventive effects, given the unique, lasting reductions in disease burden after limited dosing of psychedelic drugs compared with conventional treatments. The results from the first controlled, clinical study of a psychedelic to treat migraine are discussed including the limitations of the trial. The overlap between psychedelic drug actions and the neurobiological pathology in headache and chronic pain disorders are also discussed, stressing the importance of distinguishing between acute and long-lasting effects. Safety issues are also covered with particular regard to the contrast between the historical use of psychedelics and more recent untested self-administration methods.

Ross et al. (2022) discuss the use of psychedelic drugs as adjuncts to psychotherapy for treating psychiatric and existential distress in life-threatening conditions and at the end-stage of life. The treatments currently used in these patient populations, including medication and psychotherapy, have limited effectiveness. The authors review efficacy results from the first and second waves of research on psychedelics and comment on future directions for research and implementation.

7. Conclusions

The 5-year period following our previous Special Issue on Psychedelics has witnessed an exponential increase in research into the psychedelics accompanied by unprecedented levels of venture capital investment in this long-running marathon to bring the classical psychedelics into approved clinical use. The contributors to this Special Issue have provided a valuable and comprehensive overview of this rapidly evolving field of pharmacological research. The Editors wish to thank all of the authors for their time, effort and excellent contributions.

Editors: David J Heal, Sharon L Smith, Sean J Belouin and Jack E Henningfield.

Date: May 2023.

Declaration of Interests and Disclaimers

David Heal and Sharon Smith are shareholders and employees of DevelRx Ltd. DevelRx provides consultancy on drug discovery and development to treat psychiatric, neurological and metabolic disorders. They specialize in advising pharmaceutical companies on drug abuse and dependence evaluations and prepare regulatory submissions. DevelRx also advises on the development and approval of psychedelics and other natural products as novel therapeutics. Professor David Heal and Dr Sharon Smith received no external financial support for writing this article, and no external commercial interests had any input.

Jack Henningfield is an employee of PinneyAssociates, Inc. which provides scientific and regulatory consulting support for new drug applications (NDAs) and risk management programs for a broad range of CNS active substances and drug products including psychedelic substances, new chemical entities, and alternative formulations and routes of delivery, as well as dietary ingredient notifications, cannabinoid assessment, and noncombustible tobacco/nicotine products for FDA regulation. Dr Henningfield received no external financial support for writing this article and no external commercial interests had any input.

Sean Belouin has no conflict of interests to declare. The views, opinions, and content of this publication are those of authors CAPT Sean J. Belouin et al. and do not necessarily reflect the views, opinions, or policies of the US Public Health Service, the US Department of Health and Human Services, the Substance Abuse and Mental Health Services administration, the National Institutes of Health, the Food and Drug Administration, the Centers for Medicare and Medicaid Services, the US Department of Justice, the Drug Enforcement Agency, the US Department of Defense, the US Department of Veterans Affairs, and/or, the World Health Organization.

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D.J. Heal*
DevelRx Ltd, BioCity, Nottingham, NG1 1GF, UK
Department of Life Sciences, University of Bath, Bath, BA2 7AY, UK

S.L. Smith
DevelRx Ltd, BioCity, Nottingham, NG1 1GF, UK
E-mail address: sharon.smith@develrx.com.

S.J. Belouin
United States Public Health Service (USPHS), Germantown, MD, USA
Substance Abuse and Mental Health Services Administration (SAMHSA), Rockville, MD, USA
NIH Clinical Research Center, Pain and Palliative Care, Bethesda, MD, USA
E-mail address: sjbelouin@gmail.com.

J.E. Henningfield
Pinney Associates, 4800 Montgomery Ln Suite 400, Bethesda, MD, 20814, USA
Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine, 5510 Nathan Shock Drive, Baltimore, MD, 21224, USA
E-mail address: jhenning@pinneyassociates.com.

* Corresponding author.
E-mail address: david.heal@develrx.com (D.J. Heal).