27 psychedelic-relevant abstracts april '19 newsletter

(Belouin and Henningfield 2018; Carhart-Harris, Bolstridge et al. 2018; Eischens and Atherton 2018; Garcia-Romeu and Richards 2018; George 2018; Girn and Christoff 2018; Griffiths, Johnson et al. 2018; Haijen, Kaelen et al. 2018; Hendricks, Crawford et al. 2018; Johnson, Hendricks et al. 2018; Jungaberle, Thal et al. 2018; Ly, Greb et al. 2018; Millière, Carhart-Harris et al. 2018; Nielson and Guss 2018; Olson 2018; Renelli, Fletcher et al. 2018; Rucker, Iliff et al. 2018; Sherwood and Prisinzano 2018; Thal and Lommen 2018; Walsh and Thiessen 2018; Anderson, Petranker et al. 2019; Carhart-Harris 2019; Davis, So et al. 2019; Domany, Bleich-Cohen et al. 2019; Martial, Cassol et al. 2019; Polito and Stevenson 2019; Strawbridge, Carter et al. 2019)

Anderson, T., R. Petranker, et al. (2019). ***"Microdosing psychedelics: Personality, mental health, and creativity differences in microdosers."*** Psychopharmacology. https://doi.org/10.1007/s00213-018-5106-2

Rationale Microdosing psychedelics—the regular consumption of small amounts of psychedelic substances such as LSD or psilocybin—is a growing trend in popular culture. Recent studies on full-dose psychedelic psychotherapy reveal promising benefits for mental well-being, especially for depression and end-of-life anxiety. While full-dose therapies include perception-distorting properties, microdosing may provide complementary clinical benefits using lower-risk, non-hallucinogenic doses. Objectives This pre-registered study aimed to investigate whether microdosing psychedelics is related to differences in personality, mental health, and creativity. Methods In this observational study, respondents recruited from online forums self-reported their microdosing behaviors and completed questionnaires concerning dysfunctional attitudes, wisdom, negative emotionality, open-mindedness, and mood. Respondents also performed the Unusual Uses Task to assess their creativity. Results Current and former microdosers scored lower on measures of dysfunctional attitudes ($p < 0.001$, $r = -0.92$) and negative emotionality ($p = 0.009$, $r = -0.85$) and higher on wisdom ($p < 0.001$, $r = 0.88$), openmindedness($p = 0.027$, $r = 0.67$), and creativity ($p < 0.001$, $r = 0.15$) when compared to non-microdosing controls. Conclusions These findings provide promising initial evidence that warrants controlled experimental research to directly test safety and clinical efficacy. As microdoses are easier to administer than full-doses, this new paradigm has the exciting potential to shape future psychedelic research.

Belouin, S. J. and J. E. Henningfield (2018). ***"Psychedelics: Where we are now, why we got here, what we must do."*** Neuropharmacology 142: 7-19. http://www.sciencedirect.com/science/article/pii/S0028390818300753

(Available in free full text) The purpose of this commentary is to provide an introduction to this special issue of Neuropharmacology with a historical perspective of psychedelic drug research, their use in psychiatric disorders, research-restricting regulatory controls, and their recent emergence as potential breakthrough therapies for several brain-related disorders. It begins with the discovery of lysergic acid diethylamide (LSD) and its promising development as a treatment for several types of mental illnesses during the 1940s. This was followed by its abuse and stigmatization in the 1960s that ultimately led to the placement of LSD and other psychedelic drugs into the most restrictively regulated drug schedule of the United States Controlled Substances Act (Schedule I) in 1970 and its international counterparts. These regulatory controls severely constrained development of psychedelic substances and their potential for clinical research in psychiatric disorders. Despite the limitations, there was continued research into brain mechanisms of action for psychedelic drugs with potential clinical applications which began during the 1990s and early 2000s. Finding pathways to accelerate clinical research in psychedelic drug development is supported by the growing body of research findings that are documented throughout this special issue of Neuropharmacology. Accumulated research to date suggests psychedelic drug assisted psychotherapy may emerge as a potential breakthrough treatment for several types of mental illnesses including depression, anxiety, post-traumatic stress disorder, and addiction that are refractory to current evidenced based therapies. This research equally shows promise in advancing the understanding of the brain, brain related functioning, and the consequential effects of untreated brain related diseases that have been implicated in causing and/or exacerbating numerous physical disease state conditions. The authors conclude that more must be done to effectively address mental illnesses and brain related diseases which have become so pervasive, destructive, and whose treatments are becoming increasingly resistant to current evidenced based therapies. This article is part of the Special Issue entitled 'Psychedelics: New Doors, Altered Perceptions'.

Carhart-Harris, R. L. (2019). ***"How do psychedelics work?"*** Current Opinion in Psychiatry 32(1): 16-21. https://journals.lww.com/co-psychiatry/Fulltext/2019/01000/How_do_psychedelics_work_.4.aspx

Purpose of review Psychedelics are reawakening interest from psychiatry, cognitive neuroscience and the general public with impressive outcomes in small-scale clinical trials, intriguing human brain imaging work and high-impact journalism. Recent findings This brief opinion piece offers a perspective on how psychedelics work in the brain that may help contextualize these developments. It attempts to link various scales of action, from the molecular (serotonin 2A receptor agonism) through to the anatomical and functional (heightened plasticity) and up to the dynamic (increased brain entropy), systems level (network disintegration and desegregation) and experiential. Summary It is proposed that psychedelics initiate a cascade of neurobiological changes that manifest at multiple scales and ultimately culminate in the relaxation of high-level beliefs. The purpose of psychedelic therapy is to harness the opportunity afforded by this belief-relaxation to achieve a healthy revision of pathological beliefs.

Carhart-Harris, R. L., M. Bolstridge, et al. (2018). ***"Psilocybin with psychological support for treatment-resistant depression: Six-month follow-up."*** Journal of Psychopharmacology 235(2): 399-408. https://doi.org/10.1007/s00213-017-4771-x

(Available in free full text) Rationale Recent clinical trials are reporting marked improvements in mental health outcomes with psychedelic drug-assisted psychotherapy. Objectives Here, we report on safety and efficacy outcomes for up to 6 months in an open-label trial of psilocybin for treatment-resistant depression. Methods Twenty patients (six females) with (mostly) severe, unipolar, treatment-resistant major depression received two oral doses of psilocybin (10 and 25 mg, 7 days apart) in a supportive setting. Depressive symptoms were assessed from 1 week to 6 months post-treatment, with the self-rated QIDS-SR16 as the primary outcome measure. Results Treatment was generally well tolerated. Relative to baseline, marked reductions in depressive symptoms were observed for the first 5 weeks post-treatment (Cohen's $d = 2.2$ at week 1 and 2.3 at week 5, both $p < 0.001$); nine and four patients met the criteria for response and remission at week 5. Results remained positive at 3 and 6 months (Cohen's $d = 1.5$ and 1.4, respectively, both $p < 0.001$). No patients sought conventional antidepressant treatment within 5 weeks of psilocybin. Reductions in depressive symptoms at 5 weeks were predicted by the

quality of the acute psychedelic experience. Conclusions Although limited conclusions can be drawn about treatment efficacy from open-label trials, tolerability was good, effect sizes large and symptom improvements appeared rapidly after just two psilocybin treatment sessions and remained significant 6 months post-treatment in a treatment-resistant cohort. Psilocybin represents a promising paradigm for unresponsive depression that warrants further research in double-blind randomised control trials.

Davis, A. K., S. So, et al. (2019). ***"5-methoxy-n,n-dimethyltryptamine (5-meo-dmt) used in a naturalistic group setting is associated with unintended improvements in depression and anxiety."*** The American Journal of Drug and Alcohol Abuse 45(2): 161-169. https://doi.org/10.1080/00952990.2018.1545024

ABSTRACT Background: A recent epidemiological study suggested that 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) used for spiritual and recreational reasons is associated with subjective improvement in depression and anxiety. Further exploration of the potential psychotherapeutic effects of 5-MeO-DMT could inform future clinical trials. Objectives: We examined self-reported improvement in depression and anxiety among people who use 5-MeO-DMT in a group setting with structured procedures guiding dose and administration of 5-MeO-DMT. Such procedures also include activities for the preparation of, and support during/following sessions, which are similar to procedures used in clinical trials of hallucinogen administration. Next, we examined whether depression or anxiety were improved following use, and whether the acute subjective effects (mystical/challenging) or beliefs about the 5-MeO-DMT experience were associated with improvements in these conditions. Methods: Respondents (n = 362; Mage = 47.7; Male = 55%; White/Caucasian = 84%) completed an anonymous web-based survey. Results: Of those reporting having been diagnosed with depression (41%) or anxiety (48%), most reported these conditions were improved (depression = 80%; anxiety = 79%) following 5-MeO-DMT use, and fewer reported they were unchanged (depression = 17%; anxiety = 19%) or worsened (depression = 3%; anxiety = 2%). Improvement in depression/anxiety conditions were associated with greater intensity of mystical experiences and higher ratings of the spiritual significance and personal meaning of the 5-MeO-DMT experience. There were no associations between depression or anxiety improvement and the intensity of acute challenging physical/psychological effects during the 5-MeO-DMT experience. Conclusions: Future prospective controlled clinical pharmacology studies should examine the safety and efficacy of 5-MeO-DMT administration for relieving depression and anxiety.

Domany, Y., M. Bleich-Cohen, et al. (2019). ***"Repeated oral ketamine for out-patient treatment of resistant depression: Randomised, double-blind, placebo-controlled, proof-of-concept study."*** The British Journal of Psychiatry 214(1): 20-26. https://www.cambridge.org/core/article/repeated-oral-ketamine-for-outpatient-treatment-of-resistant-depression-randomised-doubleblind-placebocontrolled-proofofconcept-study/76898B0B3980372F9EE79043F55A08FD

(Available in free full text) Background Ketamine has been demonstrated to improve depressive symptoms. Aims Evaluation of efficacy, safety and feasibility of repeated oral ketamine for out-patients with treatment-resistant depression (TRD). Method In a randomised, double-blind, placebo-controlled, proof-of-concept trial, 41 participants received either 1 mg/kg oral ketamine or placebo thrice weekly for 21 days (ClinicalTrials.gov Identifier: NCT02037503). Evaluation was performed at baseline, 40 and 240 min post administration and on days 3, 7, 14 and 21. The main outcome measure was change in Montgomery–Åsberg Depression Rating Scale (MADRS). Results Twenty-two participants were randomised to the ketamine group, and 19 to the control, with 82.5% (n = 33) completing the study. In the ketamine group, a decrease in depressive symptoms was evident at all time points, whereas in the control group a decrease was evident only 40 min post administration. The reduction in MADRS score on day 21 was 12.75 in the ketamine group versus 2.49 points with placebo ($P < 0.001$). Six participants in the ketamine group (27.3%) achieved remission compared with none of the controls ($P < 0.05$). The number needed to treat for remission was 3.7. Side-effects were mild and transient. Conclusions Repeated oral ketamine produced rapid and persistent amelioration of depressive symptoms in out-patients with TRD, and was well tolerated. These results suggest that add-on oral ketamine may hold significant promise in the care of patients suffering from TRD in the community.

Eischens, P. and W. L. Atherton (2018). ***"Psychedelic therapy as a complementary treatment approach for alcohol use disorders."*** Journal of Psychedelic Studies 2(1): 36-44. https://akademiai.com/doi/abs/10.1556/2054.2018.005

Background Traditional treatment interventions for alcohol use disorders (AUD) have produced mixed outcomes and the global increase in AUDs demands novel and innovative approaches to addiction treatment. Psychedelic substances have been reintroduced into the Western medical community as a potential intervention to complement the treatment of AUDs. Objectives This paper will discuss the implications of using psychedelic substances as a complementary approach within the treatment of AUDs. Methods A thorough review of pertinent research focused on the use of psychedelics in relation to the affective, cognitive, social, legal, and spiritual issues commonly associated with AUDs. Results Research suggests the clinical efficacy and safety of psychedelic therapy as a complementary treatment for AUDs. Conclusion Future directions and implications to AUD treatment are provided.

Garcia-Romeu, A. and W. A. Richards (2018). ***"Current perspectives on psychedelic therapy: Use of serotonergic hallucinogens in clinical interventions."*** International Review of Psychiatry 30(4): 291-316. https://doi.org/10.1080/09540261.2018.1486289

Abstract Humans have used serotonergic hallucinogens (i.e. psychedelics) for spiritual, ceremonial, and recreational purposes for thousands of years, but their administration as part of a structured therapeutic intervention is still a relatively novel practice within Western medical and psychological frameworks. In the mid-20th century, considerable advances were made in developing therapeutic approaches integrating administration of low (psycholytic) and high (psychedelic) doses of serotonergic hallucinogens for treatment of a variety of conditions, often incorporating psychoanalytic concepts prevalent at that time. This work contributed seminal insights regarding how these substances may be employed with efficacy and safety in targeted therapeutic interventions, including the importance of optimizing set (frame of mind) and setting (therapeutic environment). More recently, clinical and pharmacological research has revisited the effects and therapeutic potential of psychedelics utilizing a variety of approaches. The current article provides an overview of past and present models of psychedelic therapy, and discusses important considerations for future interventions incorporating the use of psychedelics in research and clinical practice.

George, M. S. (2018). ***"Is there really nothing new under the sun? Is low-dose ketamine a fast-acting antidepressant simply because it is an opioid?"*** Am J Psychiatry 175(12): 1157-1158. https://ajp.psychiatryonline.org/doi/abs/10.1176/appi.ajp.2018.18070800

(Available in free full text) Psychiatrists are now dealing with three "epidemics" that have a profound impact on society—opioid dependence, depression, and suicide. We desperately need new treatments for depression, and for suicidality, while also reducing opioid dependence and abuse. In the setting of this "triple crunch" and the frantic search for breakthrough treatments, low-dose intravenous ketamine has emerged as a potentially rapid-acting antidepressant that also quickly reduces suicidality. Could the universe be so cruel as to make it so that a treatment for one or two of the epidemics actually fuels the

other? Thus, the article by Williams and colleagues (1) in this issue has potentially broad clinical and social implications, as it raises questions about all three. In this small-sample single-center crossover trial, these innovative Stanford researchers asked a simple but important question: Do the rapid antidepressant effects of ketamine depend on activation of opioid receptors? Specifically, can you block the antidepressant effect of ketamine by pretreatment with naltrexone, an opioid blocker? They asked this question in part because the other main pharmacological action of ketamine, N-methyl-D-aspartate (NMDA) receptor antagonism, has largely failed to emerge as the necessary mechanism of action for ketamine's antidepressant effects. The answer seems clear from this trial, which was stopped early because the distinct answer emerged with only half the projected sample. Pretreating with naltrexone dramatically blocked the antidepressant effect of ketamine, but it did not block the dissociation that many subjects experience. That is, ketamine's acute antidepressant effect appears to require opioid system activation. The succinct and logical conclusion from the research is that opioid receptors are necessary for ketamine's acute antidepressant effect.

Girn, M. and K. Christoff (2018). ***"Expanding the scientific study of self-experience with psychedelics."*** Journal of Consciousness Studies 25: 131-154. https://www.ingentaconnect.com/contentone/imp/jcs/2018/00000025/f0020011/art00008

The nature of the self has long been a topic of discussion in philosophical and religious contexts, and has recently also garnered significant scientific attention. Although evidence exists to suggest the multifaceted nature of self-experience, the amount of research done on each of its putative components has not been uniform. Whereas selfreflective processing has been studied extensively, non-reflective aspects of self-experience have been the subject of comparatively little empirical research. This discrepancy may be linked to the methodological difficulties in experimentally isolating the latter. Recent work suggests that one potential way to overcome these difficulties is through the experimentally-controlled administration of psychedelic substances that have the ability to reliably alter non-reflective aspects of self-experience. Here, we review what we know so far about the phenomenology of alterations in self-experience that occur as a result of the administration of psychedelics. We also introduce a taxonomy of such alterations in terms that can bridge contemporary cognitive neuroscience and research on psychedelics. We conclude that the scientific understanding of self-experience may be significantly advanced by expanding experimental paradigms and theoretical accounts to incorporate work with psychedelic substances.

Griffiths, R. R., M. W. Johnson, et al. (2018). ***"Psilocybin-occasioned mystical-type experience in combination with meditation and other spiritual practices produces enduring positive changes in psychological functioning and in trait measures of prosocial attitudes and behaviors."*** Journal of Psychopharmacology (Oxford, England) 32(1): 49-69. https://www.ncbi.nlm.nih.gov/pubmed/29020861 https://www.ncbi.nlm.nih.gov/pmc/PMC5772431/

(Available in free full text) Psilocybin can occasion mystical-type experiences with participant-attributed increases in well-being. However, little research has examined enduring changes in traits. This study administered psilocybin to participants who undertook a program of meditation/spiritual practices. Healthy participants were randomized to three groups (25 each): (1) very low-dose (1 mg/70 kg on sessions 1 and 2) with moderate-level ("standard") support for spiritual-practice (LD-SS); (2) high-dose (20 and 30 mg/70 kg on sessions 1 and 2, respectively) with standard support (HD-SS); and (3) high-dose (20 and 30 mg/70kg on sessions 1 and 2, respectively) with high support for spiritual practice (HD-HS). Psilocybin was administered double-blind and instructions to participants/staff minimized expectancy confounds. Psilocybin was administered 1 and 2 months after spiritual-practice initiation. Outcomes at 6 months included rates of spiritual practice and persisting effects of psilocybin. Compared with low-dose, high-dose psilocybin produced greater acute and persisting effects. At 6 months, compared with LD-SS, both high-dose groups showed large significant positive changes on longitudinal measures of interpersonal closeness, gratitude, life meaning/purpose, forgiveness, death transcendence, daily spiritual experiences, religious faith and coping, and community observer ratings. Determinants of enduring effects were psilocybin-occasioned mystical-type experience and rates of meditation/spiritual practices. Psilocybin can occasion enduring trait-level increases in prosocial attitudes/behaviors and in healthy psychological functioning.

Haijen, E. C. H. M., M. Kaelen, et al. (2018). ***"Predicting responses to psychedelics: A prospective study."*** Frontiers in Pharmacology 9(897). https://www.frontiersin.org/article/10.3389/fphar.2018.00897

(Available in free full text) Responses to psychedelics are notoriously difficult to predict, yet significant work is currently underway to assess their therapeutic potential and the level of interest in psychedelics among the general public appears to be increasing. We aimed to collect prospective data in order to improve our ability to predict acute- and longer-term responses to psychedelics. Individuals who planned to take a psychedelic through their own initiative participated in an online survey (www.psychedelicsurvey.com). Traits and variables relating to set, setting and the acute psychedelic experience were measured at five different time points before and after the experience. Principle component and regression methods were used to analyse the data. Sample sizes for the five time points included N= 654, N= 535, N= 379, N= 315, and N= 212 respectively. Psychological well-being was increased two weeks after a psychedelic experience and remained at this level after four weeks. This increase was larger for individuals who scored higher for a 'mystical-type experience', and smaller for those who scored higher for 'challenging experience'. Having 'clear intentions' for the experience was conducive to mystical-type experiences. Having a positive 'set', as well as having the experience with intentions related to 'recreation', were both found to decrease the likelihood of having a challenging experience. The trait 'absorption' and higher drug doses promoted both mystical-type and challenging experiences. When comparing different types of variables, traits variables seemed to explain most variance in the change in well-being after a psychedelic experience. These results confirm the importance of extra-pharmacological factors in determining responses to a psychedelic. We view this study as an early step towards the development of empirical guidelines that can evolve and improve iteratively with the ultimate purpose of guiding crucial clinical decisions about whether, when, where and how to dose with a psychedelic, thus helping to reduce risks while maximising potential benefits in an evidence-based manner.

Hendricks, P. S., M. S. Crawford, et al. (2018). ***"The relationships of classic psychedelic use with criminal behavior in the united states adult population."*** Journal of Psychopharmacology 32(1): 37-48. https://journals.sagepub.com/doi/abs/10.1177/0269881117735685

Criminal behavior exacts a large toll on society and is resistant to intervention. Some evidence suggests classic psychedelics may inhibit criminal behavior, but the extent of these effects has not been comprehensively explored. In this study, we tested the relationships of classic psychedelic use and psilocybin use per se with criminal behavior among over 480,000 United States adult respondents pooled from the last 13 available years of the National Survey on Drug Use and Health (2002 through 2014) while controlling for numerous covariates. Lifetime classic psychedelic use was associated with a reduced odds of past year larceny/theft (aOR = 0.73 (0.65–0.83)), past year assault (aOR = 0.88 (0.80–0.97)), past year arrest for a property crime (aOR = 0.78 (0.65–0.95)), and past year arrest for a violent crime (aOR = 0.82 (0.70–0.97)). In contrast, lifetime illicit use of other drugs was, by and large, associated with an increased odds of these outcomes. Lifetime classic psychedelic use, like lifetime illicit use of almost all other substances, was associated with an increased odds of past year drug distribution. Results

were consistent with a protective effect of psilocybin for antisocial criminal behavior. These findings contribute to a compelling rationale for the initiation of clinical research with classic psychedelics, including psilocybin, in forensic settings.

Johnson, M. W., P. S. Hendricks, et al. (2018). ***"Classic psychedelics: An integrative review of epidemiology, mystical experience, brain network function, and therapeutics."*** Pharmacology & Therapeutics. http://www.sciencedirect.com/science/article/pii/S0163725818302158

The purpose of this paper is to provide an integrative review and offer novel insights regarding human research with classic psychedelics (classic hallucinogens), which are 5HT2AR agonists such as lysergic acid diethylamide (LSD), mescaline, and psilocybin. Classic psychedelics have been administered as sacraments since ancient times. They were of prominent interest within psychiatry and neuroscience in the 1950s to 1960s, and during this time contributed to the emergence of the field of molecular neuroscience. Promising results were reported for treatment of both end-of-life psychological distress and addiction, and classic psychedelics served as tools for studying the neurobiological bases of psychological disorders. Moreover, classic psychedelics were shown to occasion mystical experiences, which are subjective experiences reported throughout different cultures and religions involving a strong sense of unity, among other characteristics. However, the recreational use of classic psychedelics and their association with the counterculture prompted an end to human research with classic psychedelics in the early 1970s. We review recent therapeutic studies suggesting efficacy in treating psychological distress associated with life-threatening diseases, treating depression, and treating nicotine and alcohol addictions. We also describe the construct of mystical experience, and provide a comprehensive review of modern studies investigating classic psychedelic-occasioned mystical experiences and their consequences. These studies have shown classic psychedelics to fairly reliably occasion mystical experiences. Moreover, classic psychedelic-occasioned mystical experiences are associated with improved psychological outcomes in both healthy volunteer and patient populations. We also review neuroimaging studies that suggest neurobiological mechanisms of psychedelics. These studies have also broadened our understanding of the brain, the serotonin system, and the neurobiological basis of consciousness. Finally, we provide the most comprehensive review of epidemiological studies of classic psychedelics to date. Notable among these are a number of studies which have suggested the possibility that nonmedical naturalistic (non-laboratory) use of classic psychedelics is associated with positive mental health and prosocial outcomes, although it is clear that some individuals are harmed by classic psychedelics in non-supervised settings. Overall, these various lines of research suggest that classic psychedelics might hold strong potential as therapeutics, and as tools for experimentally investigating mystical experiences and behavioral-brain function more generally.

Jungaberle, H., S. Thal, et al. (2018). ***"Positive psychology in the investigation of psychedelics and entactogens: A critical review."*** Neuropharmacology 142: 179-199. http://www.sciencedirect.com/science/article/pii/S0028390818303368

Rationale We reviewed the concepts and empirical findings in studies with psychedelics and entactogens related to positive psychology – the study of healthy human functioning, well-being and eudaemonia. It is an unresolved question how beneficial effects of psychedelics and entactogens are related to the potential risks of these substances – particularly in non-clinical settings. Methods We searched in PubMed, PsychINFO and the Cochrane Library for controlled clinical and epidemiological studies which applied concepts from positive psychology. We included N = 77 eligible studies with 9876 participants published before November 1st, 2017: (1) quantitative studies (N = 54), (2) preliminary or exploratory studies and reviews not including meta-analyses (N = 17), and (3) studies evidencing primarily negative results (N = 6). Results Positive psychology concepts have been applied for measuring effects of clinical trials, recreational and ceremonial use of psychedelics and entactogens. Psychedelics and entactogens were shown to produce acute and long-term effects on mood, well-being, prosocial behaviours, empathy, cognitive flexibility, creativity, personality factors like openness, value orientations, nature-relatedness, spirituality, self-transcendence and mindfulness-related capabilities. Conclusions There is preliminary evidence for beneficial effects of psychedelics and entactogens on measures of positive psychology in clinical and healthy populations, however their sustainability remains largely unresolved. The reported results must be considered preliminary due to methodological restrictions. Since longitudinal data on both positive and adverse effects of psychedelics are lacking, more rigorous and standardized measures from positive psychology should be applied in less biased populations with prospective longitudinal designs to carefully assess the benefit-risk-ratio. This article is part of the Special Issue entitled 'Psychedelics: New Doors, Altered Perceptions'.

Ly, C., A. C. Greb, et al. (2018). ***"Psychedelics promote structural and functional neural plasticity."*** Cell Rep 23(11): 3170-3182. https://www.ncbi.nlm.nih.gov/pubmed/29898390

Atrophy of neurons in the prefrontal cortex (PFC) plays a key role in the pathophysiology of depression and related disorders. The ability to promote both structural and functional plasticity in the PFC has been hypothesized to underlie the fast-acting antidepressant properties of the dissociative anesthetic ketamine. Here, we report that, like ketamine, serotonergic psychedelics are capable of robustly increasing neuritogenesis and/or spinogenesis both in vitro and in vivo. These changes in neuronal structure are accompanied by increased synapse number and function, as measured by fluorescence microscopy and electrophysiology. The structural changes induced by psychedelics appear to result from stimulation of the TrkB, mTOR, and 5-HT2A signaling pathways and could possibly explain the clinical effectiveness of these compounds. Our results underscore the therapeutic potential of psychedelics and, importantly, identify several lead scaffolds for medicinal chemistry efforts focused on developing plasticity-promoting compounds as safe, effective, and fast-acting treatments for depression and related disorders.

Martial, C., H. Cassol, et al. (2019). ***"Neurochemical models of near-death experiences: A large-scale study based on the semantic similarity of written reports."*** Consciousness and Cognition 69: 52-69. http://www.sciencedirect.com/science/article/pii/S105381001830535X

(Available in free full text on Researchgate) The real or perceived proximity to death often results in a non-ordinary state of consciousness characterized by phenomenological features such as the perception of leaving the body boundaries, feelings of peace, bliss and timelessness, life review, the sensation of traveling through a tunnel and an irreversible threshold. Near-death experiences (NDEs) are comparable among individuals of different cultures, suggesting an underlying neurobiological mechanism. Anecdotal accounts of the similarity between NDEs and certain drug-induced altered states of consciousness prompted us to perform a large-scale comparative analysis of these experiences. After assessing the semantic similarity between ≈15,000 reports linked to the use of 165 psychoactive substances and 625 NDE narratives, we determined that the N-methyl-D-aspartate (NMDA) receptor antagonist ketamine consistently resulted in reports most similar to those associated with NDEs. Ketamine was followed by Salvia divinorum (a plant containing a potent and selective κ receptor agonist) and a series of serotonergic psychedelics, including the endogenous serotonin 2A receptor agonist N,N-Dimethyltryptamine (DMT). This similarity was driven by semantic concepts related to consciousness of the self and the environment, but also by those associated with the therapeutic, ceremonial and religious aspects of drug use. Our analysis sheds light on the long-standing link between certain drugs and the experience of "dying", suggests that ketamine could be used as a safe and reversible experimental model for NDE phenomenology, and supports the speculation that endogenous NMDA antagonists with

neuroprotective properties may be released in the proximity of death. [See https://tinyurl.com/y2tomvf6 for helpful BPS Research Digest discussion of this paper].

Millière, R., R. L. Carhart-Harris, et al. (2018). ***"Psychedelics, meditation, and self-consciousness."*** Frontiers in psychology 9: 1475-1475. https://www.ncbi.nlm.nih.gov/pubmed/30245648 https://www.ncbi.nlm.nih.gov/pmc/PMC6137697/

(Available in free full text) In recent years, the scientific study of meditation and psychedelic drugs has seen remarkable developments. The increased focus on meditation in cognitive neuroscience has led to a cross-cultural classification of standard meditation styles validated by functional and structural neuroanatomical data. Meanwhile, the renaissance of psychedelic research has shed light on the neurophysiology of altered states of consciousness induced by classical psychedelics, such as psilocybin and LSD, whose effects are mainly mediated by agonism of serotonin receptors. Few attempts have been made at bridging these two domains of inquiry, despite intriguing evidence of overlap between the phenomenology and neurophysiology of meditation practice and psychedelic states. In particular, many contemplative traditions explicitly aim at dissolving the sense of self by eliciting altered states of consciousness through meditation, while classical psychedelics are known to produce significant disruptions of self-consciousness, a phenomenon known as drug-induced ego dissolution. In this article, we discuss available evidence regarding convergences and differences between phenomenological and neurophysiological data on meditation practice and psychedelic drug-induced states, with a particular emphasis on alterations of self-experience. While both meditation and psychedelics may disrupt self-consciousness and underlying neural processes, we emphasize that neither meditation nor psychedelic states can be conceived as simple, uniform categories. Moreover, we suggest that there are important phenomenological differences even between conscious states described as experiences of self-loss. As a result, we propose that self-consciousness may be best construed as a multidimensional construct, and that "self-loss," far from being an unequivocal phenomenon, can take several forms. Indeed, various aspects of self-consciousness, including narrative aspects linked to autobiographical memory, self-related thoughts and mental time travel, and embodied aspects rooted in multisensory processes, may be differently affected by psychedelics and meditation practices. Finally, we consider long-term outcomes of experiences of self-loss induced by meditation and psychedelics on individual traits and prosocial behavior. We call for caution regarding the problematic conflation of temporary states of self-loss with "selflessness" as a behavioral or social trait, although there is preliminary evidence that correlations between short-term experiences of self-loss and long-term trait alterations may exist.

Nielson, E. M. and J. Guss (2018). ***"The influence of therapists' first-hand experience with psychedelics on psychedelic-assisted psychotherapy research and therapist training."*** Journal of Psychedelic Studies 2(2): 64-73. https://akademiai.com/doi/abs/10.1556/2054.2018.009

(Available in free full text) Clinical research on psychedelic-assisted psychotherapy is rapidly advancing in the USA, with two drugs, psilocybin and MDMA, progressing through a structure of FDA-approved trials on a trajectory toward Drug Enforcement Agency rescheduling for therapeutic use. Researcher's and clinician's personal use of psychedelics was cited as a potential confound in psychedelic research studies conducted in the 1950s and 1960s, a concern which contributed to the cessation of this research for some 20 years. Currently, there is no empirical research on personal use of psychedelics by current academic researchers and clinicians; its influence is undocumented, unknown, and undertheorized. This paper explores the history of personal use of psychedelics by clinicians and researchers, the potential impact of personal use on psychedelic-assisted psychotherapy and research, and the rationale for opening an academic discussion and program of research to investigate the role of personal use. We propose that there are factors unique to psychedelic-assisted therapy such that training for it cannot neatly fit into the framework of modern psychopharmacology training, nor be fully analogous to psychotherapy training in contemporary psychological and psychiatric settings. We argue that scientific exploration of the influence of therapists' first-hand experience of psychedelics on psychedelic-assisted therapy outcomes is feasible, timely, and necessary for the future of clinical research.

Olson, D. E. (2018). ***"Psychoplastogens: A promising class of plasticity-promoting neurotherapeutics."*** Journal of Experimental Neuroscience 12: 1179069518800508. https://journals.sagepub.com/doi/abs/10.1177/1179069518800508

Neural plasticity—the ability to change and adapt in response to stimuli—is an essential aspect of healthy brain function and, in principle, can be harnessed to promote recovery from a wide variety of brain disorders. Many neuropsychiatric diseases including mood, anxiety, and substance use disorders arise from an inability to weaken and/or strengthen pathologic and beneficial circuits, respectively, ultimately leading to maladaptive behavioral responses. Thus, compounds capable of facilitating the structural and functional reorganization of neural circuits to produce positive behavioral effects have broad therapeutic potential. Several known drugs and experimental therapeutics have been shown to promote plasticity, but most rely on indirect mechanisms and are slow-acting. Here, I describe psychoplastogens—a relatively new class of fast-acting therapeutics, capable of rapidly promoting structural and functional neural plasticity. Psychoplastogenic compounds include psychedelics, ketamine, and several other recently discovered fast-acting antidepressants. Their use in psychiatry represents a paradigm shift in our approach to treating brain disorders as we focus less on rectifying "chemical imbalances" and place more emphasis on achieving selective modulation of neural circuits.

Polito, V. and R. J. Stevenson (2019). ***"A systematic study of microdosing psychedelics."*** PLOS ONE 14(2): e0211023. https://doi.org/10.1371/journal.pone.0211023

(Available in free full text) The phenomenon of 'microdosing', that is, regular ingestion of very small quantities of psychedelic substances, has seen a rapid explosion of popularity in recent years. Individuals who microdose report minimal acute effects from these substances yet claim a range of long-term general health and wellbeing benefits. There have been no published empirical studies of microdosing and the current legal and bureaucratic climate makes direct empirical investigation of the effects of psychedelics difficult. In Study One we conducted a systematic, observational investigation of individuals who microdose. We tracked the experiences of 98 microdosing participants, who provided daily ratings of psychological functioning over a six week period. 63 of these additionally completed a battery of psychometric measures tapping mood, attention, wellbeing, mystical experiences, personality, creativity, and sense of agency, at baseline and at completion of the study. Analyses of daily ratings revealed a general increase in reported psychological functioning across all measures on dosing days but limited evidence of residual effects on following days. Analyses of pre and post study measures revealed reductions in reported levels of depression and stress; lower levels of distractibility; increased absorption; and increased neuroticism. To better understand these findings, in Study Two we investigated pre-existing beliefs and expectations about the effects of microdosing in a sample of 263 naïve and experienced microdosers, so as to gauge expectancy bias. All participants believed that microdosing would have large and wide-ranging benefits in contrast to the limited outcomes reported by actual microdosers. Notably, the effects believed most likely to change were unrelated to the observed pattern of reported outcomes. The current results suggest that dose controlled empirical research on the impacts of microdosing on mental health and attentional capabilities are needed.

Renelli, M., J. Fletcher, et al. (2018). ***"An exploratory study of experiences with conventional eating disorder treatment and ceremonial ayahuasca for the healing of eating disorders."*** Eat Weight Disord. https://doi.org/10.1007/s40519-018-0619-6

PURPOSE: Ayahuasca is a traditional Amazonian medicine that is currently being researched for its potential in treating a variety of mental disorders. This article reports on exploratory qualitative research relating to participant experiences with ceremonial ayahuasca drinking and conventional treatment for eating disorders (EDs). It also explores the potential for ayahuasca as an adjunctive ED treatment. METHODS: Thirteen individuals previously diagnosed with an ED participated in a semi-structured interview contrasting their experiences with conventional ED treatment with experiences from ceremonial ayahuasca. The interviews were analyzed using thematic analysis. RESULTS: Participant reports were organized with key themes including that ayahuasca: led to rapid reductions in ED thoughts and symptoms; allowed for the healing of the perceived root of the ED; helped to process painful feelings and memories; supported the internalization of greater self-love and self-acceptance; and catalyzed spiritual elements of healing. CONCLUSIONS: The results suggest that ayahuasca may have potential as a valuable therapeutic tool, and further research-including carefully controlled clinical trials-is warranted. LEVEL OF EVIDENCE: Level V, qualitative descriptive study.

Rucker, J. J. H., J. Iliff, et al. (2018). ***"Psychiatry & the psychedelic drugs. Past, present & future."*** Neuropharmacology 142: 200-218. http://www.sciencedirect.com/science/article/pii/S002839081730638X

(Available in free full text) The classical psychedelic drugs, including psilocybin, lysergic acid diethylamide and mescaline, were used extensively in psychiatry before they were placed in Schedule I of the UN Convention on Drugs in 1967. Experimentation and clinical trials undertaken prior to legal sanction suggest that they are not helpful for those with established psychotic disorders and should be avoided in those liable to develop them. However, those with so-called 'psychoneurotic' disorders sometimes benefited considerably from their tendency to 'loosen' otherwise fixed, maladaptive patterns of cognition and behaviour, particularly when given in a supportive, therapeutic setting. Pre-prohibition studies in this area were sub-optimal, although a recent systematic review in unipolar mood disorder and a meta-analysis in alcoholism have both suggested efficacy. The incidence of serious adverse events appears to be low. Since 2006, there have been several pilot trials and randomised controlled trials using psychedelics (mostly psilocybin) in various non-psychotic psychiatric disorders. These have provided encouraging results that provide initial evidence of safety and efficacy, however the regulatory and legal hurdles to licensing psychedelics as medicines are formidable. This paper summarises clinical trials using psychedelics pre and post prohibition, discusses the methodological challenges of performing good quality trials in this area and considers a strategic approach to the legal and regulatory barriers to licensing psychedelics as a treatment in mainstream psychiatry. This article is part of the Special Issue entitled 'Psychedelics: New Doors, Altered Perceptions'.

Sherwood, A. M. and T. E. Prisinzano (2018). ***"Novel psychotherapeutics – a cautiously optimistic focus on hallucinogens."*** Expert Review of Clinical Pharmacology 11(1): 1-3. https://doi.org/10.1080/17512433.2018.1415755

(Available in free full text) Disrupted mental health affects up to one in three individuals globally and is an unmet medical challenge contributing to individual suffering as well as significant societal and economic burden. In response to the stalled development of new drugs and a greater than ever need for novel therapies to treat psychiatric illness, the last two decades have seen renewed scientific and medical receptiveness to the idea of treating several mental disorders with drugs commonly known as hallucinogens. 'Hallucinogens,' in a general sense, define a vast and diverse set of molecules that elicit significant alteration in human consciousness by acting on targets in the central nervous system, temporarily rerouting synaptic transmission in the brain. Commonly accepted classes of hallucinogens include psychedelics, entactogens, dissociatives, and atypical hallucinogens that include deliriants, cannabinoids, and kappa opioids. Each class possesses its own unique attributes and subclasses as well as some degree of overlap with regard to perceived effects, pharmacology, and/or potential therapeutic utility. The therapeutic use of hallucinogens represents a potentially new paradigm in the way medicine understands and treats psychiatric illnesses. While the pharmacological diversity of hallucinogens is vast, a fascinating common phenomenon has been observed in their therapeutic utility: a single acute exposure to the hallucinogenic agent can elicit an immediate and lasting improvement in symptoms for the patient, an effect that persists long after the drug is metabolized and gone from the body. This is in contrast to current pharmacotherapies used to treat mental disorders, such as selective serotonin reuptake inhibitors (SSRIs), which are based on a therapeutic model that attempts to alleviate symptoms by re-equilibrating the steady-state levels of serotonin in the brain using a chronic dosing regimen of the drug. The evolution of novel therapies to treat psychiatric conditions is inevitable as new tools and technologies contribute to our understanding of the intricate mechanics of the brain. Unquestionably, the hallucinogen's unique ability to perturb consciousness provides a compelling tool to help understand the connectivity of the brain in relation to the genesis of self-awareness and introspection. While the molecular pharmacology of most hallucinogens has been established, the complementary biological mechanisms responsible for their observed effects on the psyche are only beginning to be understood. As more rigorous scientific data emerges from clinical research, combined with the availability of modern brain-imaging techniques, we are provided with newly generated insight into the mind. This insight will provide a foundation and rationale for the way that we understand the brain, ultimately leading to the development of novel approaches to treating mental illness.

Strawbridge, R., B. Carter, et al. (2019). ***"Augmentation therapies for treatment-resistant depression: Systematic review and meta-analysis."*** The British Journal of Psychiatry 214(1): 42-51. https://www.cambridge.org/core/article/augmentation-therapies-for-treatmentresistant-depression-systematic-review-and-metaanalysis/0FEA123FDECE5FB2E838517DC22F8C57

(Available in free full text) Background Depression is considered to have the highest disability burden of all conditions. Although treatment-resistant depression (TRD) is a key contributor to that burden, there is little understanding of the best treatment approaches for it and specifically the effectiveness of available augmentation approaches. Aims We conducted a systematic review and meta-analysis to search and quantify the evidence of psychological and pharmacological augmentation interventions for TRD. Method Participants with TRD (defined as insufficient response to at least two antidepressants) were randomised to at least one augmentation treatment in the trial. Pre-post analysis assessed treatment effectiveness, providing an effect size (ES) independent of comparator interventions. Results Of 28 trials, 3 investigated psychological treatments and 25 examined pharmacological interventions. Pre-post analyses demonstrated N-methyl-d-aspartate-targeting drugs to have the highest ES (ES = 1.48, 95% CI 1.25–1.71). Other than aripiprazole (four studies, ES = 1.33, 95% CI 1.23–1.44) and lithium (three studies, ES = 1.00, 95% CI 0.81–1.20), treatments were each investigated in less than three studies. Overall, pharmacological (ES = 1.19, 95% CI 1.08–1.30) and psychological (ES = 1.43, 95% CI 0.50–2.36) therapies yielded higher ESs than pill placebo (ES = 0.78, 95% CI 0.66–0.91) and psychological control (ES = 0.94, 95% CI 0.36–1.52). Conclusions Despite being used widely in clinical practice, the evidence for augmentation treatments in TRD is sparse. Although pre-post meta-analyses are limited by the absence of direct comparison, this work finds promising evidence across treatment modalities.

Thal, S. B. and M. J. J. Lommen (2018). ***"Current perspective on mdma-assisted psychotherapy for posttraumatic stress disorder."*** Journal of Contemporary Psychotherapy 48(2): 99-108. https://doi.org/10.1007/s10879-017-9379-2

(Available in free full text) The present paper discusses the current literature with regard to substance-assisted psychotherapy with Methylenedioxymethamphetamine (MDMA) for posttraumatic stress disorder (PTSD). The aim of the paper is to give a comprehensive overview of the development from MDMA's early application in psychotherapy to its present and future role in the treatment of PTSD. It is further attempted to increase the attention for MDMA's therapeutic potential by providing a thorough depiction of the scientific evidence regarding its theorized mechanism of action and potential harms of its application in the clinical setting (e.g., misattribution of therapeutic gains to medication instead of psychological changes). Empirical support for the use of MDMA-assisted psychotherapy, including the randomized, double-blind, placebo-controlled trails that have been conducted since 2008, is discussed. Thus far, an overall remission rate of 66.2% and low rates of adverse effects have been found in the six phase two trials conducted in clinical settings with 105 blinded subjects with chronic PTSD. The results seem to support MDMA's safe and effective use as an adjunct to psychotherapy. Even though preliminary studies may look promising, more studies of its application in a psychotherapeutic context are needed in order to establish MDMA as a potential adjunct to therapy.

Walsh, Z. and M. S. Thiessen (2018). ***"Psychedelics and the new behaviourism: Considering the integration of third-wave behaviour therapies with psychedelic-assisted therapy."*** International Review of Psychiatry 30(4): 343-349. https://doi.org/10.1080/09540261.2018.1474088

Abstract This narrative review examines evidence related to the potential for third wave behaviour therapies to serve as adjuncts to psychedelic-assisted therapy. It identifies shared theoretical foundations for both approaches, and notes enhanced mindfulness, decentering, emotion regulation, and distress tolerance as common mechanisms of action. It also identifies potential targets for which both approaches have demonstrated therapeutic potential, including problematic substance use, self-directed and other-directed violence, and mood disorders. Based on these commonalities, there is a call for research on the potential integration of psychedelic-assisted therapy and third wave behaviour therapies including Dialectical Behaviour Therapy, Acceptance and Commitment Therapy, and Mindfulness Based Cognitive Therapy.