The Dynamic Field of Psychedelic Medical Research:

A Review of Recent Developments

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Introduction

The blossoming global interest in psychedelic science has its original roots in the emergence of psychedelic-assisted psychotherapy from the late 1940s to the early 1970s, as the potential of these drugs to enhance therapeutic outcomes was explored. Research and clinical practice in the field diminished dramatically in response to the global War on Drugs, as legal restrictions and social stigma came to dominate the landscape.

Following a thirty-year hiatus, interest has steadily returned as investigators have gradually overcome social and academic conservatism, research funding has become available from a range of sources, and government sanctions on psychedelic research have been relaxed.

During the intervening period, from the 1970s to the early 2000s, psychedelic science was largely relegated to the arcane domain of a fringe community, which nonetheless included experienced, dedicated (and patient) clinicians and researchers who were ideally poised to lead the psychedelic revival as it gathered pace in the early years of the current millennium.

Since 2010, the "mainstreaming" of psychedelics has gathered momentum as unprecedented media attention – almost entirely positive – has illuminated the renaissance in psychedelic medical research, informing Western society of the potential of psychedelic drugs as therapeutic adjuncts and agents of personal transformation.

Historical Perspective

Various plant-derived psychoactive compounds, notably psilocybin, mescaline, N,N-dimethyltryptamine (DMT), ibogaine, and some tropane alkaloids, have been used in ritual and spiritual contexts in various parts of the world for hundreds, possibly thousands, of years. Some of those ritual uses continue to the present day.

At the dawn of modern medicinal chemistry, mescaline was first isolated, characterised and bioassayed by Arthur Heffter, a German pharmacologist and chemist, in 1897. However, it was the discovery of the psychoactive effects of LSD in 1943 that unequivocally started the modern age of psychedelics. First synthesised in 1938 by Dr Albert Hofmann of Sandoz Laboratories, LSD led to rapid advancements in neuroscience, such as the identification and elucidation of the serotonin neurotransmitter system. This led to a significant shift in psychiatry, as numerous medicines were developed based on this new understanding of the brain.

In the context of psychotherapy, LSD itself was also found to be effective in the treatment of a range of mental disorders, including addiction, anxiety and depression. Just one or two sessions of LSD-assisted psychotherapy were found to produce profound, rapid, long-lasting positive effects with little need for further interventions, unlike psychoanalysis which involved years of therapy. Grinspoon and Bakalar stated in 1997 that "between 1950 and the mid-1960s … more than a thousand clinical papers discussing 40,000 patients" had been published along with "several dozen books, and six international conferences discussing psychedelic therapy".

The widespread non-clinical use of LSD soon became associated with the counterculture movement of the 60s, and opposition to the US military involvement in Vietnam. In an effort to curb the perceived destabilisation of American society, US President Richard Nixon made LSD and other psychedelic drugs (e.g. mescaline, psilocybin and DMT) illegal - despite their demonstrated safety profile and in the face of concerted efforts by psychologists and psychiatrists to allow them to

continue using LSD in a therapeutic context. This was the start of Nixon's "War on Drugs", supported by the international ratification of the United Nations 1971 Convention on Psychotropic Substances, and consequently led to a halt in psychedelic treatments and research. A propaganda campaign exaggerating the dangers of LSD was initiated by the Nixon government, containing misinformation that persisted for almost 45 years.

Meanwhile, 3,4-methylenedioxymethamphetamine (MDMA) emerged as an adjunct to psychotherapy in the 1970s, to enhance couples relationship counselling and to address trauma. Later, in the early 1980s, the drug's euphoric effects were noted more broadly by the general community, and in response to increasing recreational use, the US Drug Enforcement Administration (DEA) sought to ban it in 1984. Judge Francis L. Young was asked by the DEA to conduct hearings to determine the most appropriate scheduling of MDMA, and following the testimony of many psychiatrists and psychologists, Young ruled that MDMA should be classed as a Schedule III medicine. However, the DEA did not take this advice and made the drug illegal in the USA by placing it in Schedule I, the same category as heroin.

It took sustained efforts on the part of a few determined individuals to recommence research in healthy volunteers from around 1990, and then initiate clinical research to treat mental health conditions around 2000. Subsequently, a widely-touted international renaissance in psychedelic science has occurred, notably in the USA, Switzerland, the UK, Canada and Israel.

There is little question that research and the clinical application of psychedelics ceased in the 1970s and 1980s due entirely to the pressure exerted by the War on Drugs. LSD, psilocybin and DMT are not dangerous when used carefully in a clinical setting. They are non-addictive and have low acute toxicity, there being no reports of death from the toxicological effects of an acute LSD, psilocybin or DMT overdose. Increasingly, the medical profession and the broader community alike are coming to recognise that due primarily to dogmatism and the systematic dissemination of misinformation, 40 precious years of potential progress in mental health research and treatment have been lost.

Recent and Current Psychedelic Research

The World Health Organization's International Clinical Trials Registry Platform (who.int/ictrp) provides details of clinical trials registered with a range of organisations around the globe. As tabulated below, the ICTRP currently lists 32 active or completed research studies involving psilocybin, eight involving LSD, one ayahuasca, four ibogaine, four salvinorin A, and 48 mechanistic studies, psychological studies and/or clinical trials involving the empathogen, MDMA. There is also a comprehensive trial just commencing at Johns Hopkins University investigating the effects of a broad range of hallucinogens and other drugs on mood and performance.

Table 1. Psilocybin Research Projects and Clinical Trials

Site	Sponsor	Focus	Sample Size	Status
Mechanism				
University of Wisconsin	Site-sponsored	Pharmacokinetics	12	Completed
Yale	Heffter Institute	Neuroplasticity in Major Depressive Disorder	18	Active, recruiting
Rigshospitalet Copenhagen	Site-sponsored	5HT2A receptor modulation	45	Active, recruiting
Czech National Institute of Mental Health	Czech Ministry of Health	Psilocybin as a model of psychotic illness	Not disclosed	Active
Mental Health Intervention				
Harbor-UCLA	Heffter	Cancer anxiety	12	Completed
Johns Hopkins	Heffter	Psychopharmacology in cancer patients	56	Completed
Imperial College London	UK Govt (MRC)	Depression	12	Completed
NYU	Site-sponsored	Cancer anxiety	32	Active, not recruiting
UCSF	Heffter River Styx Stupski Usona	Group therapy for AIDS survivors	36	Active, not recruiting
Yale University	Heffter	Obsessive-Compulsive Disorder	30	Active, recruiting
Johns Hopkins	Site-sponsored	Major Depressive Disorder	24	Active, recruiting
Johns Hopkins	Beckley, Heffter	Nicotine dependence	95	Active, recruiting
University of Alabama, Birmingham	Site-sponsored	Cocaine dependence	40	Active, recruiting
New York University	NYU, Heffter, UNM	Alcohol dependence	180	Active, recruiting
University of New Mexico	Heffter	Alcohol dependence	10	Active, not recruiting
University of Arizona	Not disclosed	Obsessive-Compulsive Disorder	15	Not yet recruiting
University of Helsinki	Site-sponsored	Depression	60	Not yet recruiting

University of Zurich	Swiss National Funds	Depression	60	Not yet recruiting
Multiple sites	Compass Pathways Ltd	Treatment-resistant Depression	398	Not yet recruiting
Imperial College London	Alexander Mosely Trust	Major Depressive Disorder	50	Not yet recruiting
Physiological Intervention				
Yale	Site-sponsored	Migraine	24	Active, recruiting
Yale	Heffter, CH-TAC	Cluster headache	24	Active, recruiting
Psychological Study/Spirituality				
Johns Hopkins	Fetzer SF Fund	Spiritual practice	75	Completed
Johns Hopkins	Site-sponsored	Pilot study in meditators	10	Completed
Johns Hopkins	US Govt (NIDA)	Persisting effects of psilocybin	12	Completed
Imperial College London	UK Govt (MRC)	Subjective intensity of psilocybin	12	Completed
Johns Hopkins	Site-sponsored	Behaviour, psychology and brain function in long-term meditators	100	Active, not recruiting
Johns Hopkins	Site-sponsored	Mood and performance	20	Active, not recruiting
University of Zurich	Site-sponsored	Dissolution of Self	140	Active, not recruiting
NYU	Site-sponsored	Religious professionals	12	Active, recruiting
Johns Hopkins	Site-sponsored	Leaders of Religion	12	Active, recruiting
University of Maastricht	Site-sponsored	Cognitive flexibility	60	Not recruiting

Table 2. LSD Research Projects and Clinical Trials

Site	Sponsor	Focus	Sample Size	Status
Mechanism				
University Hospital, Basel	Site-sponsored	Physiological & psychological effects	16	Completed
University Hospital, Basel	Site-sponsored	Neuronal correlates of Altered States of Consciousness	24	Completed
University Hospital, Basel	Site-sponsored	Role of dopamine, serotonin and 5-HT2A receptors in emotion processing	28	Completed
University Hospital, Basel	Site-sponsored	Role of 5-HT2A receptor in Altered States of Consciousness	16	Active, recruiting
Mental Health Intervention				
Peter Gasser MD	MAPS	Illness-related anxiety	12	Completed
University Hospital, Basel	Site-sponsored	Anxiety	40	Active, recruiting
Psychological Study/Spirituality				
University of Zurich	Site-sponsored	Role of 5-HT2A receptor in perception of self and personal meaning	25	Completed
University Hospital, Basel	Site-sponsored	Altered States of Consciousness elicited by LSD & psilocybin	40	Not yet recruiting

Table 3. Ayahuasca Research Projects and Clinical Trials

Site	Sponsor	Focus	Sample Size	Status
Mental Health Intervention				
Universidade Federal do Rio Grande do Norte	University of Sao Paulo	Antidepressant effects	35	Active, not recruiting

Table 4. Ibogaine Research Projects and Clinical Trials

Site	Sponsor	Focus	Sample Size	Status
Mechanism				
University of Otago		CYP2D6 pharmacokinetics	24	Completed
Mental Health Intervention				
Instituto Veracruz de Pesquisa e Tratamento de Dependencia Quimica, Brazil		Cardiac safety of ibogaine treatment of cocaine and crack addiction	70	Not yet recruiting
University of Sao Paulo		Alcohol dependence	12	Not yet recruiting

Table 5. Salvinorin A Research Projects and Clinical Trials

Site	Sponsor	Focus	Sample Size	Status
Mechanism				
Yale	National Alliance for Research on Schizophrenia & Depression	Effects in healthy controls	41	Active, not recruiting
California Pacific Medical Centre	Site-sponsored	Pharmacodynamic and tolerability study	8	Active, not recruiting
Johns Hopkins	Site-sponsored	Effect on brain function	20	Active, recruiting
Psychological Study				
Johns Hopkins	US Govt (NIDA)	Human psychopharmacology	14	Active, not recruiting

Table 6. MDMA Research Projects and Clinical Trials

Site	Sponsor	Focus	Sample Size	Status
Mechanism & Physiology				
University Hospital Basel	Site-sponsored	Effects of Methylphenidate, Modafinil, and MDMA on Emotion-processing in Humans: A Pharmaco-fMRI Study	24	Completed
University of Auckland	Site-sponsored	MDMA (3,4-methylenedioxy-N-methylamphetamine) and tinnitus	40	Completed
Parc de Salut Mar	National Institute on Drug Abuse	Methylenedioxymethamphetamine (MDMA, Ecstasy) Induced Changes in Drug Metabolism: Gender and Genetic Polymorphisms	27	Completed
California Pacific Medical Center Research Institute	Site-sponsored	Study of the Effects of MDMA/Ecstasy on Water Regulation, Sleep, and Cognition.	12	Completed
Dept. of Nuclear Medicine, Hadassah Hospital	Hadassah Medical Organization	Functional Brain Imaging in Recreational Users of Ecstasy	18	Completed
University Hospital Basel	Site-sponsored	Pharmacological Interaction Between Clonidine and Methylenedioxymethamphetamine (MDMA)	16	Completed
University Hospital Basel	Site-sponsored	Pharmacological Interaction Between Doxazosin and Methylenedioxymethamphetamine (MDMA)	16	Completed
University Hospital Basel	Site-sponsored	Interaction Between Duloxetine and 3,4-Methylenedioxymethamphetamine (MDMA, Ecstasy)	16	Completed
University Hospital Basel	Site-sponsored	Pharmacological Interaction Between Carvedilol and Methylenedioxymethamphetamine (MDMA)	16	Completed

University Hospital Basel	Heffter	Pharmacological Interaction Between Pindolol and MDMA (3,4-Methylenedioxymethamphetamine)	16	Completed
University Hospital Basel	Site-sponsored	Interaction Between Reboxetine and 3,4-Methylenedioxymethamphetamine: Pharmacodynamics (PD) and Pharmacokinetics (PK)	16	Completed
University Hospital of Psychiatry, Zurich	Site-sponsored	Investigation of Serotonin Neurotransmission in MDMA Users Using Combinated Dexfenfluramine Challenge and PET Imaging	50	Completed
University Hospital Basel	Site-sponsored	Influence of Bupropion on the Effects of MDMA	16	Completed
University Maastricht	Netherlands Organization for Scientific Research	MDMA en prosociaal gedrag: De rol van de 2a-serotonine receptor.	20	Active, recruiting
UCSF	MAPS	MDMA in Subjects With Moderate Hepatic Impairment and Subjects With Normal Hepatic Function	16	Not yet recruiting
Yale	Site-sponsored	The Effects of MDMA on Prefrontal and Amygdala Activation in PTSD	20	Not yet recruiting
Mental Health Intervention				
Michael Mithoefer MD	MAPS	MDMA-assisted and Cognitive-Behavioral Conjoint Therapy (CBCT) in Dyads With One Member With Chronic PTSD	12	Completed
Philip Wolfson MD	MAPS	MDMA-assisted Psychotherapy for Anxiety Associated With a Life-threatening Illness	18	Completed
Los Angeles Biomedical Research Institute	MAPS	MDMA-assisted Therapy for Social Anxiety in Autistic Adults	12	Completed
Dr Ingrid Pacey	MAPS	Randomized, Double-blind, Controlled of MDMA-assisted Psychotherapy in 12 Subjects With PTSD	6	Completed
Marcela Ot'alora	MAPS	Dose-Response Study of MDMA-assisted Psychotherapy in People With PTSD	27	Completed

Beer Yaakov Mental Health Center	MAPS	Randomized, Double-blind, Active-placebo Controlled Study of MDMA-assisted Psychotherapy in People With Chronic PTSD	10	Completed
Michael Mithoefer MD	MAPS	Additional MDMA-assisted Psychotherapy for People Who Relapsed After MDMA-assisted Psychotherapy Trial	3	Completed
Michael Mithoefer MD	MAPS	Study Comparing Three Doses of MDMA Along With Psychotherapy in Veterans With Posttraumatic Stress Disorder	26	Completed
Peter Oehen MD	MAPS	Study of 3,4-Methylenedioxymethamphetamine-assisted Psychotherapy in People With Posttraumatic Stress Disorder	14	Completed
Michael Mithoefer MD	MAPS	A Test of MDMA-Assisted Psychotherapy in People With Posttraumatic Stress Disorder	23	Completed
Instituto Plantando Consciência - Sao Paulo, SP, Brazil	MAPS	MDMA-assisted psychotherapy in the treatment of trauma	4	Active, not recruiting
Marcela Ot'alora	MAPS	Psychological Effects of Methylenedioxymethamphetamine (MDMA) When Administered to Healthy Volunteers	100	Active, enrolling by invitation
Multiple sites	MAPS	A Multi-Site Phase 3 Study of MDMA-Assisted Psychotherapy for PTSD	100	Recruiting
Dr Simon Amar	MAPS	Study of Safety and Effects of MDMA-assisted Psychotherapy for Treatment of PTSD	5	Recruiting
Multiple sites	MAPS	Open Label Multi-Site Study of Safety and Effects of MDMA-assisted Psychotherapy for Treatment of PTSD	60	Recruiting
Imperial College London	Alexander Mosley Charitable Trust	Exploring MDMA in psychotherapy in detoxified patients with alcohol dependency syndrome	Not specified	Authorised
University Maastricht	MAPS	Een studie naar de veiligheid en effecten van psychotherapie in	Not specified	Not yet recruiting

		combinatie met MDMA als behandeling voor zware post-traumatische stress stoornis		
Beer Yaakov Mental Health Center	MAPS	Randomized Placebo-controlled Study of MDMA-assisted Psychotherapy in People With PTSD - Israel	12	Terminated
Brigham & Women's Hospital	Site-sponsored	MDMA-assisted Therapy in People With Anxiety Related to Advanced Stage Cancer	2	Terminated
Psychological Study				
University of Chicago	National Institute on Drug Abuse	Effects of MDMA on Social and Emotional Processing	65	Completed
University Hospital Basel	Site-sponsored	Effects of MDMA and Methylphenidate on Social Cognition	30	Completed
University Hospital Basel	Site-sponsored	Emotional Effects of Methylphenidate and MDMA in Healthy Subjects	16	Completed
University Hospital Basel	Site-sponsored	Role of Dopamine, Serotonin and 5-HT2A Receptors in Emotion Processing	28	Completed
Michael Mithoefer MD	MAPS	Exploring Mechanisms of Action in MDMA-assisted Psychotherapy for PTSD	10	Completed
California Pacific Medical Center Research Institute	Site-sponsored	Role of Serotonin in Acute and Subacute MDMA Effects	13	Completed
University of Chicago	Site-sponsored	Effects of MDMA on Emotional and Social Memories	60	Active, not recruiting
University Maastricht	Site-sponsored	MDMA and memory.	16	Active, not recruiting
Emory University	MAPS	Evaluation of MDMA on Startle Response	30	Active, recruiting
Michael Mithoefer MD	MAPS	Psychological Effects of Methylenedioxymethamphetamine (MDMA) When Administered to Healthy Volunteers	100	Active, recruiting
University Maastricht	Netherlands Organization	MDMA, Cortisol and Memory	60	Active, recruiting

	for Scientific Research			
University Hospital Basel	Site-sponsored	Effect of Methylenedioxymethamphetamine (MDMA) (Serotonin Release) on Fear Extinction	30	Not yet recruiting
University Maastricht	Netherlands Organization for Scientific Research	MDMA and prosocial behavior.	18	Not yet recruiting

These summary tables of recent psychedelic research highlight that MDMA and psilocybin are the compounds being most extensively studied, by a considerable margin. The conditions for which these drugs are being investigated overlap slightly, although psilocybin is being more widely studied for anxiety and depression, including when experienced in association with terminal prognosis. Psilocybin has also shown efficacy in the treatment and prevention of cluster headaches, treatment of Obsessive-Compulsive Disorder, and in cessation of the problematic use of substances including tobacco, alcohol and stimulants. MDMA is proving effective as an adjunct to psychotherapy primarily, and most specifically, for the treatment of post-traumatic stress disorder (PTSD), and social anxiety in adults on the autism spectrum.

The following discussion reviews the key interventional clinical trials undertaken within the last 10-15 years, many of which are completed but some of which are ongoing.

Depression

Depression is one of the most common mental illnesses experienced globally. An estimated 5.8% of Australians (i.e. around 123,000 people) experience a major depressive episode in any year, while 30% of men and 40% of women will experience Major Depressive Disorder in their lifetime. While numerous psychotherapeutic interventions are effective for depression, not all people respond to these treatments. Often such individuals are placed on medications or even treated with Electroconvulsive Therapy, but these interventions also have limited success. This not only has an enormous impact on the quality of life for these individuals, but given the high prevalence of the disorder, it creates a significant economic burden to the healthcare system and also to the economy more broadly, given treatment-refractory depression impacts people's ability to work.

A 2016 review of psychedelic-assisted psychotherapy for depression by Rucker et al examined 21 studies published between 1949 and 1973. While they noted that many of the studies had methodological limitations, with sample sizes ranging from 5 to 77, and only four studies including a control group, they concluded there is some evidence that psychedelic-assisted psychotherapy could be an effective treatment and that given the growing costs of depression within the community, this treatment should be re-investigated by way of RCTs.

A psychedelic neuroscience research program has been established at Imperial College in London, where an RCT among 20 healthy participants with no history of mental illness demonstrated that a dose of LSD improved people's mood, optimism and the personality trait of openness for at least two weeks without causing any long-term psychological harm. A subsequent open-label trial of psilocybin-assisted therapy among 12 participants with treatment-resistant depression showed promising results, eliciting a significant improvement in eight of the participants (67%) who no longer met DSM criteria for depressive symptoms one week after the psilocybin session. Hedge's g was 3.1 indicating a strong effect. While some participants had relapsed at three-month follow-up, there was still a significant reduction in the mean Beck Depression Inventory scores and, interestingly, a significant reduction in participants' State-Trait Anxiety scores was observed from baseline to follow-up.

The Imperial College researchers have proposed that these psychotherapeutic benefits are due to inactivation of the Default Mode Network (DMN) by psilocybin and other psychedelic drugs. The DMN is a group of interconnected brain regions associated with self-referent processing and rumination, and brain imaging has shown that DMN activation diminishes while people are having a psychedelic experience. In addition, these researchers have also observed increased interconnectivity among areas of the brain that are normally segmented. This might allow people to perceive themselves and the world with a new perspective. Indeed, in the open-label trial of people with treatment-refractory depression, lead researcher Carhart-Harris noted that those participants who remained in remission at 3 month follow-up were most likely to have had the most significant deactivation of the DMN during their psilocybin session.

Research using psychedelic drugs might also enhance other psychotherapeutic interventions. The Imperial College research group has also shown that LSD enhances suggestibility. In a clinical setting, this property of LSD could be used effectively to change entrenched ways of thinking that have not responded to psychotherapeutic interventions such as those among people with treatment-resistant depression, but also a range of conditions including some personality disorders and anxiety disorders. In a 2015 study by Barrett et al, LSD was shown to enhance emotional responses to music, which could be harnessed to improve the efficacy of psychotherapeutic interventions.

Ayahuasca has also been examined as a treatment for depression. In addition to the psychological aspect of the ayahuasca experience, it appears that there is also a pharmacological explanation for why ayahuasca could be effective as a treatment for depression. Callaway et al found in 1994 that members of a syncretic Brazilian church that uses ayahuasca had an increased number of serotonin platelet binding sites compared to the matched controls. Low density of serotonin receptors has been associated with depression and suicide. In a 2015 open-label trial by Osorio et al, six Brazilian participants with a diagnosis of recurrent Major Depressive Disorder were administered a single dose of ayahuasca. Hamilton Depression Rating Scale (HDRS) scores decreased by 62% within 24 hours, and by day 7 the scores had decreased by 72%. While there was a small increase in HDRS scores at day 14, they were still lower than at baseline and the HDRS scores on day 21 were similar to those on day 7. A systematic review conducted in 2016 by dos Santos et al examined 21 studies of the effects of ayahuasca on anxiety and depression. They concluded that the studies consistently show that "... [ayahuasca has] anxiolytic and antidepressive properties". One study they reviewed showed that it was an effective treatment for treatment-refractory depression.

Palliative care

People with terminal illness often experience a range of negative psychological symptoms such as depression and anxiety, which in turn lead to a further decrease in their quality of life. For example, a 2011 meta-analysis by Mitchell et al found that among patients with cancer, 30% - 40% met DSM-IV criteria for a range of mood and anxiety disorders. Given that antidepressants have low efficacy among people with cancer, psychologists are increasingly being asked to assist patients to manage these symptoms with the aim of improving their quality of life. However, systematic reviews of psychosocial interventions for people receiving palliative care found few interventions that improved patient satisfaction; many only demonstrated small effect sizes for improvement in quality of life, and the evidence for improved psychological functioning was limited. Meanwhile, through a collaboration between Johns Hopkins Medical School and UCLA, research has found that psilocybin-assisted psychotherapy is effective at reducing anxiety and improving the quality of life for people suffering end-stage cancer. An initial Phase 2 study was conducted under the direction of Dr Charles Grob at Harbor-UCLA, and yielded promising results. Two further RCTs of psilocybin-assisted psychotherapy for psychosocial distress associated with terminal illness were published in 2016, and are discussed below.

The first was a crossover study by Ross et al in which 16 participants were randomised to a niacin control condition, since niacin can create some facial flushing and other physiological effects, and 15 participants to the psilocybin condition. The psychotherapy protocol involved three 2-hour preparatory sessions with a male-female clinical team to establish a therapeutic alliance, review the meaning and nature of the psychological and existential distress associated with participants' cancer and collaboratively develop specific management plans (psychotherapeutic and pharmacological) to minimise any psychologically adverse effects of psilocybin. The psilocybin/niacin session occurred in a lounge room-like environment where participants were encouraged to lie comfortably on a couch wearing eye shades, listening to pre-selected music through headphones (standardised to be the same for all participants and selected by the research team to temporally match the phenomenological effects of psilocybin over its course of action) and directing their attention to their internal experience. The therapists were present throughout the entire 8-hour session. Towards the end of the session, participants were encouraged to discuss the entirety of their subjective experience with the treatment team to consolidate the memory of it and begin the integration process. Over the following weeks, participants completed three 2-hour post-integrative sessions that aimed to further consolidate the memory and continue the process of psychological integration. The post-integrative sessions took an informed-eclectic approach, utilising cognitive-behavioural therapy, existential psychotherapy and psychodynamic/psychoanalytic-oriented therapies.

Ross et al found that from baseline to one day post the first psilocybin session, 83% of participants in the psilocybin group (cf. 14% in the niacin group) met criteria for an anti-depressant response according to the Beck Depression Inventory, while 58% of participants in the psilocybin group met criteria for anxiolytic response using the HADS Anxiety subscale (cf. 14% in the niacin-first group). Participants in the psilocybin arm also had lower state and trait anxiety one day post the first psilocybin session compared to the control group, and reported improvements in their physical health and social relationships as measured by the World Health Organisation Quality of Life Scale - Brief Version from baseline to 2 weeks post the psilocybin session compared to the control group. All

of the effects were large with Cohen's d ranging between 0.8 and 1.69, with almost all effects greater than 1.0. These effects were sustained for seven weeks post the first psilocybin session. The crossover occurred at week 7 with participants in the control arm receiving a psilocybin session while participants in the psilocybin arm received a second psilocybin session. Similar acute effects were observed among the crossover group when they received psilocybin. The effects among the first psilocybin group were maintained at a 26-week follow-up.

The second study, by Griffiths et al, was a double-blind RCT of 56 end-stage cancer patients in which a low dose of psilocybin was used as a control. The psychotherapy protocol was similar to that described by Ross et al. Those in the high dose condition had significant reductions in several measures of anxiety and depression (e.g., Beck Depression Inventory, Hamilton Anxiety Rating Scale, Brief Symptom Inventory, etc.), and improved quality of life as measured by the McGill Quality of Life Scale, compared to the low dose group (effect sizes ranged between 0.35 and 1.33, with a mean effect size of 0.82, as measured using Cohen's d). Once all participants had received a high dose, a 6-month follow-up showed that the reductions in anxiety and depression were maintained with comparisons to baseline showing effect sizes ranging between 0.66 and 2.98.

Post-traumatic Stress Disorder

Post-traumatic Stress Disorder (PTSD) is a debilitating psychiatric condition arising after a traumatic life event that severely reduces quality of life and may lead to or exacerbate other psychiatric and medical problems. PTSD is considered a worldwide public health issue. It is estimated that 1.2% of Australians will have PTSD in any 12 month period. In 2010, PTSD was the most prevalent anxiety disorder in the Australian Defence Force, affecting 8.3% of members. There has been recent media interest in this issue as more Australian soldiers, particularly young men, are now losing their lives through suicide than have died in recent conflicts.

PTSD is clearly a serious public health problem and contributes substantially to healthcare costs. PTSD is typically a chronic illness associated with high rates of psychiatric and medical co-morbidity, disability, suffering and suicide. People experiencing PTSD face challenges in relationships and work productivity. Yet questions remain concerning the best possible treatments.

When exposure-based psychotherapeutic interventions for PTSD work, they work well. The average client who completes prolonged exposure therapy has an 86% greater reduction in symptoms than a wait-list control participant, and these changes are maintained in long term follow-ups. However, it has been estimated at least 30% of people do not respond to exposure-based psychotherapeutic interventions. For example, in a Randomised Control Trial (RCT) of Cognitive Processing Therapy that recruited 171 rape victims, there was an attrition rate of 30%, and of those who completed treatment, 47% still met criteria for PTSD. Many of these clients drop out of treatment as they find the exposure too confronting, cannot talk about the trauma, or do not engage in the exposure enough for the treatment to be effective (i.e. the window of tolerance). Those who do not respond to psychotherapeutic interventions are typically treated with antidepressant medications to attenuate the symptoms, though this treatment has low efficacy and the medications can cause side effects.

3,4-Methylenedioxymethamphetamine (MDMA) was first synthesised by Merck and patented in 1913 as an intermediate compound in the search for an effective drug to control bleeding. MDMA is

not strictly classified as a psychedelic; better described as an entactogen or empathogen, it was used in psychotherapy in the 1970s as an adjunct in couples relationship counselling and to help address trauma - it has the unique properties of creating empathy with clinical staff, allowing the client to re-experience the traumatic event within the window of tolerance, and overcome survivor's guilt. The first clinical study reporting on the therapeutic effects of MDMA was published in 1986 by Greer and Tolbert.

Despite oft-cited concerns about the safety of MDMA, there have been no serious adverse events in any of the clinical studies completed so far. One very well controlled study in Utah by Halpern et al recruited 52 people who used Ecstasy (an early colloquial name for MDMA) regularly and 59 people who had never used the drug. All participants were not to have used any other substance, including alcohol, in their lifetime, and were members of the club/rave scene. The researchers found no significant differences on a range of neuropsychological tests.

Despite initial promising results, an initial study of MDMA as an adjunct to psychotherapy in the treatment of PTSD by Bouso et al in 2000 was shut down by the Spanish government. The first RCT looking at the efficacy of MDMA-assisted psychotherapy for treatment-refractory PTSD commenced in 2001 and found that after 12 sessions of psychotherapy, with just two MDMA sessions, 83% of participants no longer met DSM-IV criteria for PTSD. These effects were maintained at a 3.5-year follow-up, with only 10% of participants relapsing in that time.

The treatment protocol involved three preparation sessions that focused on building a therapeutic alliance between the client and the male-female co-therapist team. It also involved an assessment of the client's existing support systems for emotional regulation and self-care, and stress inoculation training was provided that built on the client's existing anxiety management strategies. The MDMA (125 mg) was then administered in a session that started in the morning and occurred in a lounge room-like setting, with "participants lying on a futon, sometimes with eyeshades and headphones listening to music with male and female therapists sitting on either side for at least eight hours". This session was far less directive than CBT, though there was an agreement that the therapists would bring up the trauma event at some point during each MDMA session if it did not come up spontaneously. During dialogue that emerged during the session, there was the opportunity to engage in cognitive restructuring, though remarkably, it was noted that the effects of MDMA alone often led the client to have profound insights about cognitive distortions spontaneously. The client stayed overnight in the clinic and an integration session occurred the next morning. It was stated that this session is essential as the objective is to consolidate the memories of the MDMA session into everyday consciousness and daily life.

After the client had left the integration session, they were contacted via phone as part of a check-in procedure. They then attended another MDMA session a few weeks later, with further integrative sessions after this MDMA session.

Later studies used three MDMA sessions and reduced the dose to 75 mg, with a Phase 2 trial completed in Switzerland and further Phase 2 trials more recently completed in South Carolina, Colorado, Canada and Israel. The sponsor of these trials is the Multidisciplinary Association for Psychedelic Studies (MAPS), a not-for-profit organisation that also administers a Public Benefit Corporation. MAPS staff met with the US Food and Drug Administration (FDA) in November 2016 and received approval to commence a Phase 3 study, the protocol for which was approved in April, 2017. Because of the large effect size of the pooled Phase 2 data, with two thirds of participants no

longer meeting criteria for PTSD, the FDA accepted a smaller sample size than typically would be required for a Phase 3 study, and there is now the potential for people to access MDMA-assisted therapy through a compassionate use scheme. This means people can now access MDMA-assisted psychotherapy without necessarily taking part in the research. The key goal of MAPS has been for MDMA to be approved as a prescription medicine in the USA by 2021; however, following the recent positive outcomes, this might occur even earlier.

Further studies are being completed by MAPS. One is an open label trial of Cognitive-Behavioural Conjoint Therapy (CBCT) integrated with MDMA-assisted psychotherapy for the treatment of chronic PTSD, in which the significant other of the person with PTSD participates in the treatment. Meanwhile, a program to train therapists in MDMA-assisted therapy has been developed that is a placebo-controlled, double-blind randomised, crossover study in which a single MDMA-assisted psychotherapy session is administered to therapists.

Autism Spectrum Disorder

Autism is a genetically-based human neurological variant. Autism is a developmental phenomenon, meaning that it begins in utero and has a pervasive influence on multiple levels of development throughout the lifespan. Autistic individuals frequently experience difficulty in the realm of social interaction. Comparative studies suggest that autistic adults, especially those who are verbal and whose autism might not be immediately recognisable to others and who are faced with strong pressure to conform to non-autistic social norms, are at greater risk for lifetime and current psychological disorders, especially social anxiety.

There are currently no FDA-approved pharmacological treatments for autistic adults with social anxiety, and conventional anti-anxiety medications lack clinical effectiveness in this population. Based on anecdotal reports, MDMA-assisted therapy may be a suitable intervention for the treatment of social anxiety in autistic adults and warrants further investigation in a randomised controlled clinical trial.

MAPS, in collaboration with the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center and Stanford University, has sponsored a randomised, double-blind, placebo-controlled exploratory pilot study with dose escalation to assess the safety and feasibility of MDMA-assisted therapy to treat social anxiety in 12 MDMA-naïve adults on the autism spectrum. Dr Charles Grob and Alicia Danforth were co-investigators for this study. The subjects were autistic adults with social anxiety, age 21 and older, who had completed two years of college-level education or comparable vocational training.

The study also obtained estimates of effect size based on two experimental MDMA-assisted therapy sessions in comparison to an inactive placebo control group. The experimental phase of the study was completed in June 2017 and the data are being analysed. If the results warrant further investigation, data from this study will be used to design additional studies.

Obsessive-Compulsive Disorder

Obsessive-Compulsive Disorder (OCD) is a chronic condition characterised by disturbing, intrusive thoughts and compulsive rituals. The illness has a lifetime prevalence of about 2.5%, therefore afflicting millions of people to various degrees. OCD has a range of comorbid symptoms, including anxiety, insomnia, and depression. A serious public health problem with significant associated morbidity and mortality, it is one of the few psychiatric conditions for which the level of suffering and the lack of available treatment still allow for the use of psycho-surgery in some countries.

Serotonin (5-HT) is widely thought to play a role in obsessive ideation and behaviour. Clinical research has also found that regulation of 5-HT receptors can relieve symptoms of OCD in some individuals. However, in spite of the development of several new treatments for this disorder, the total elimination of symptoms is rare.

Several individual case reports over thirty years noted beneficial effects of serotonergic psychedelics in the treatment of obsessive thoughts, leading to the hypothesis that psilocybin administered in controlled clinical environments may relieve the symptoms of obsessive compulsive disorder in some individuals. Some reports have suggested that remission of the symptoms of OCD may continue for several months after a single dose of psilocybin.

The hypothesis was tested in one Phase 1 double-blind RCT at the University of Arizona, in which varying doses of psilocybin were administered to nine participants. The results were encouraging but not conclusive, in that transient remission from symptoms was experienced by all participants, but only one participant experienced measureable remission for longer than 1-2 weeks post-dose.

Recently, two double-blind, placebo-controlled studies of psilocybin for OCD have been registered. The first, a Phase 1 study at Yale University, aims to recruit 30 participants and compare 25 mg psilocybin to 250 mg niacin placebo. The second, a Phase 2 quadruple-blind randomised dose-response study of 15 participants, will be conducted by the University of Arizona team as a follow-up to the original Phase 1. Both are in the very early stages of recruitment and are anticipated to be completed by 2021.

Migraine & Cluster Headache

Cluster headaches are a rare, severely painful form of headache that is related to but different from the more common migraine. The pain of a cluster headache commences quickly, without warning, and reaches a crescendo within 2 to 15 minutes. It is often excruciating in intensity, and is deep, non-fluctuating, and explosive in quality. People may have episodic or chronic cluster headaches; current research is focusing on the episodic form. Episodic cluster headaches occur periodically, often occurring at the same time each year. During a cycle, a person with episodic cluster headaches will experience an average of one to three headaches per day, with frequency ranging from one headache every other day to eight per day.

Conventional treatments include treatments for stopping headache pain as it occurs (abortives), and treatments that reduce the occurrence or re-occurrence of cluster headaches (prophylaxis). Case reports over many years have suggested that ingesting psilocybin or LSD can reduce cluster headache pain and, more significantly, can interrupt cluster headache cycles so that no more headaches will occur.

MAPS sponsored an early study of psilocybin for cluster headache, which is now being followed up with a Phase 1 RCT at Yale University. The study is expected to conclude in 2021.

Substance Use Disorders

In a large Australian prospective multisite study of clients accessing Alcohol and Other Drug (AOD) treatment services, 70% completed a 12-month follow-up assessment, of which 47% had not reduced their consumption of AODs. Project MATCH was a multisite study conducted over 8 years in the USA that found no difference in treatment outcomes among people seeking treatment for alcohol dependence who were randomly allocated to Cognitive-Behavioural Therapy, Motivational Interviewing or 12-step programs. This has led many to propose that addiction is a chronic and relapsing condition and that there is no one effective intervention. However, research conducted prior to the prohibition of LSD using small sample sizes found LSD-assisted psychotherapy to be effective. For example, among 16 people with severe alcohol dependence, Chwelos et al reported in 1959 that 15 had reduced their use of alcohol at a six-month follow-up, while 10 had remained abstinent.

New research is reinforcing the case that psychedelic medicines might be effective in the treatment of substance-use disorders. For example, an open-label trial of psilocybin-assisted psychotherapy for the treatment of tobacco addiction among 15 people found 10 (or 67%) were biologically confirmed as abstinent at 12-month follow-up. This is high considering that a 2009 RCT of Varenicline, the most efficacious pharmacotherapy for smoking cessation, conducted by Igarashi et al found that only 25.5% of participants were abstinent at 12 months. A proof-of-concept study has found similar effects in treating alcohol dependence with psilocybin-assisted psychotherapy showing similarly impressive effects. There was a significant reduction in alcohol consumption at week 4 of the therapy when psilocybin was administered, and this reduction was maintained for 36 weeks. The team at Johns Hopkins is now recruiting 40 participants to conduct a RCT to gather further evidence for this therapy while a team at New York University is recruiting 140 participants to examine the efficacy of psilocybin-assisted psychotherapy for alcohol dependence.

Some evidence is emerging that using the shamanic brew ayahuasca, which is typically administered in a ceremonial group context, may be an effective treatment for substance use disorders. Ayahuasca contains DMT, which is normally deactivated in the stomach and throughout the body by monoamine oxidase enzymes. By combining plants containing DMT with plants containing reversible inhibitors of monoamine oxidase-A, South American shamans have used ayahuasca for spiritual and healing purposes for hundreds, and possibly thousands, of years. In the past decade there has been an exponential increase in the number of studies published internationally, examining ayahuasca from a range of perspectives, with observational studies finding ayahuasca might assist people experiencing substance use disorders.

For example, an observational study by Thomas et al in Canada recruited 18 people who had not previously consumed ayahuasca and planned to attend an ayahuasca retreat to address their addiction to either tobacco, alcohol, cannabis, or cocaine. Participants were administered a battery of psychometric instruments prior to attending the retreat and then re-administered these scales for 5 months post the retreat. The 4-week Substance Use Scale showed that self-reported use of all substances except cannabis was significantly reduced from baseline to follow-up. Interestingly, they

also observed significant increases in measures of quality of life and hope, empowerment and mindfulness. Further research is needed to determine the efficacy of ayahuasca as a treatment for addiction.

Finally, it has long been observed that many people who develop opiate use disorders have a history of trauma. For example, Teesson et al reported in 2015 that 41% of people receiving treatment for heroin dependence met criteria for PTSD. However, some have suggested that the rates of trauma among all people with other substance use disorders may be similar. Among a sample of 423 Dutch people with a range of substance use disorders, Gielen et al reported in 2012 that 46.2% of participants whose primary drug of choice was alcohol met criteria for PTSD.

A proof-of-concept study, initiated in 2016 in the UK by Dr Ben Sessa, aims to provide an alternative treatment for people with substance use disorders who have a history of trauma. The rationale for his study is that trauma-related symptoms lead people to become socially isolated, so instead of attaching to others, people with trauma-related symptoms attach to substances. Through integrating motivational interviewing with MDMA-assisted psychotherapy, Sessa anticipates that participants will have increased positive social connectivity as a result of decreased trauma-related symptoms leading to abstinence from their drug of choice.

Mechanistic research on the therapeutic benefits of psychedelic compounds

As outlined above, contemporary research on psychedelics is corroborating historical reports of their anxiolytic and antidepressant effects. An understanding of the molecular mechanisms underpinning the therapeutic benefits of psychedelic compounds may be useful in expanding their application in psychiatry, and for research institutions, legislators and funding bodies to acknowledge their utility.

A recent study elucidated some of those molecular mechanisms. In this research, the psychedelic compounds psilocybin, DMT and DOI (a psychedelic amphetamine) were observed to promote structural and functional neural plasticity *in vitro* and *in vivo*, in a manner similar to that elicited by ketamine, a dissociative anaesthetic that is also being investigated for its antidepressant properties. The main findings included increased formation of neural interconnections, specifically through the processes of neuritogenesis, spinogenesis and synaptogenesis. It was proposed that these changes are driven by increased release of brain-derived neurotrophic factor (BDNF), a protein that activates mTOR, a key signalling cascade that regulates neuronal plasticity and which is modulated by standard antidepressant and anti-neurodegenerative drugs. Given the observed effects on neuroplasticity and immunomodulatory pathways, it is conceivable that psychedelics could prove useful in treating diseases in which neurodegeneration is implicated, such as Alzheimer's and Parkinson's disease. While extensive further studies will be necessary to validate these findings, the rationale is compelling for expanding psychedelic research to the treatment of neurodegenerative conditions.

Conclusion

The many examples tabulated and discussed in this review illustrate that psychedelic science is indeed undergoing an impressive renaissance, as broadly dispersed research groups study the

mechanistic, psychological and therapeutic effects of MDMA, psilocybin, LSD and several other compounds. In particular, the therapeutic potential of MDMA for PTSD and for social anxiety associated with autism, and likewise the potential of psilocybin as an adjunct to psychotherapy for the treatment of anxiety and depression, OCD and substance use disorders, are especially promising.

There is little doubt that the body of psychedelic medical research will continue to grow, as long as funding sources continue to support the research endeavour, regulatory authorities continue to allow this clinical and translational research to occur, and the research results ultimately confirm the early promise of these interventions.

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https://www.researchgate.net/publication/323773002_Should_Australian_Psychology_Consider_Enhancing_Psychotherapeutic_Interventions_with_Psychedelic_Drugs_A_Call_for_Research