The History of Psychedelics in Medicine

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Inhalt

Abstract

Psychedelics have been used for hundreds if not thousands of years by humans. Medical research began in earnest in the West in the late nineteenth century with the discovery of mescaline. From there we saw the development of LSD in the 1940s and an increasingly important role played by psychedelics in the 1950s in the subsequent development of biological psychiatry. Psychiatry explored psychedelic therapies extensively through to the end of the 1960s when LSD was banned. Then, other drugs emerged, notably MDMA, which took abroadly similar path to LSD; being banned in the mid-1980s. However, since then, whilst the debate around recreational uses of drugs continues, there has been a resurgence of psychedelic research in the last two decades. We now see many hundreds of new publications coming from mainstream institutions around the world studying psychedelic drugs. The history of the development of psychedelics in medicine is intimately tied-in with societal, technological and cultural changes and continues to evolve.

Keywords

LSD • Psilocybin • MDMA • Mescaline • Psychotherapy • Medicine • Psychiatry

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1 Introduction

The trajectory taken by psychedelic drugs from archaic to modern times is in its infancy. Despite 100 years of experimental data, millions of positive experiences and huge enthusiasm from the psychedelic community, there are still no licensed medical applications for *any* of the classical psychedelic drugs or entactogens anywhere in the world. This is a sobering point. *Why*, after all this time and effort, have we still not achieved the goal? The answer to that question is complex. But one way forward is to learn from history and particularly the mistakes and successes of pioneers in the field.

The *name* we use for psychedelics has evolved over the ages. Different terms, including "hallucinogens" (to induce hallucinations), "psychotomimetics" (to mimic psychosis), "psychotogenics" (to induce a psychosis), "psycholytics" (to "loosen the mind"), "psychedelics" (to "manifest mind") and "entheogens" (to generate the divine within) reflect the varying medical and societal attitudes to drugs. Psychedelics have been employed as adjuncts to psychotherapy for a wide range of psychological problems from anxiety and affective disorders to addictions. The drugs themselves have many different psychopharmacological actions and it is the combination of these psychological and biological effects, together with the environmental, sociological and personal aspects of the drug user (bulked together as "set and setting") that accounts for the totality of the experience. This colossal range of effects and applications provides the interested clinician with a versatile clinical pharmacopeia.

Grappling with the variety of applications for psychedelics has been a challenge for the medical profession; developing in tandem with technological and societal changes. And they continue to be refined. After all, no new medicine arises *de novo* in our profession with a fully developed treatment protocol. Health professionals have so much more to learn about how psychedelics can best be employed for our patients. Until then we must make do with our history.

2 The History of Psychedelics in Medicine

2.1 The Pre-Victorian Times

In Europe, rudimentary physicians since the Middle Ages have used psychotropic plants such as Belladonna, Henbane, and Mandrake Root to treat a range of mental and physical disorders (Schultes et al. 1979). Often maligned as witches by the emerging Christian beliefs, these pagan uses of psychedelic drugs were systematically eliminated.

2.2 The 1890s

In the late nineteenth century a revival of interest in non-ordinary states of consciousness leads the German pharmacologist Louis Lewin to conduct a scientific

analysis of the peyote cactus. He provides one of the earliest classifications of psychoactive drug properties, coining the terms "euphoriants" (for opiates), "inebriants," (for alcohol) and "phantastica," which later become the psychedelics (Lewin 1894). Peyote's psychological effects on humans is explored further by the American neurologist, S. Weir Mitchell (Weir Mitchell 1896) and in two papers from the British physician Henry Havelock Ellis: "The Phenomena of Mescal Intoxication" and "Mescal: A New Artificial Paradise" (Havelock Ellis 1897, 1898). A major breakthrough comes in 1897 with the isolation of the active component mescaline from the peyote cactus by German pharmacologist Arthur Carl Wilhelm Heffter, arguably the forefather of modern psychopharmacology (Heffter 1898).

2.3 1900–1920

William James, brother of the famous American novelist, publishes *The Varieties of Religious Experience*, describing his experiences with nitrous oxide and the value of altered states of consciousness (James 1902). And in 1912, the German pharmaceutical company Merck synthesises and patents 3,4 Methylenedioxymethamphetamine (MDMA), which is then shelved until the mid fifties. Meanwhile MDA, a close cousin of MDMA, is developed as an appetite suppressant under the name "Amphedoxamine" (Iversen 2006). In 1919, Austrian chemist Ernst Späth first synthesises mescaline (Späth 1919) and in 1927 German chemist, Kurt Beringer, experimenting with synthetic mescaline, proposes one of the earliest models for psychosis based on the psychedelic experience (Beringer 1927), whilst in Chicago, Heinrich Klüver uses mescaline to explore eidetic imagery (Klüver 1928).

2.4 1930s

Synthetic mescaline is readily available in the 1930s, and Walter Frederking explores it as a tool for psychotherapy (Frederking 1955). Interestingly, an Austrian novelist and mathematician, Leo Perutz, publishes a story in 1933 about a scientist who discovers a psychotropic drug based on wheat fungi used for mass spiritual transformation (Piper 2013). This fictional story pre-dates *by 5 years* Albert Hofmann's investigations of the vasoconstrictor properties of ergot at Sandoz Laboratories in Switzerland, which lead to the synthesis of LSD-25. Pharmacological experiments are subsequently conducted on LSD-25 by Professor Ernst Rothlin at Sandoz but the product is then shelved (Hofmann 1979).

2.5 1940s

Seeking a biological theory for schizophrenia, psychiatrist Tayleur Stockings experiments with mescaline as a possible psychotomimetic (Stockings 1940). Then, in 1943, Hofmann synthesises a new batch of LSD, accidentally absorbs some crystals

and has the world's first LSD experience. A few days later he conducts a personal experiment. Monitored by colleagues he intentionally ingests 250 micrograms and famously cycles back to his house from the laboratory. LSD is investigated with phase one studies that demonstrate its low toxicity and safety for human consumption. Dozens of staff members at the Sandoz laboratories are tested (Hagenbach and Werthmuller 2013). Using Lewin's term "phantastica" as a classification for the drug, Hofmann's colleague Werner Stoll, son of the Sandoz director, Arthur Stoll, publishes the first academic description of the mental effects of LSD on humans. He gives LSD to 6 schizophrenic patients and 16 controls at doses of 25–130 mcg (Stoll 1947).

Sandoz makes LSD available to psychiatrists worldwide under the name *Delysid* and in 1949 the Swiss psychiatrist Gion Condrau, gives it to a wide range of patients, including those with schizophrenia, proposing it has antidepressant effects (Condrau 1949). Carl Jung hears about LSD from Dr. Nicholas Bercel of the University of Southern California Medical School, after Bercel takes it in Basel in 1949. Allegedly, Jung never took it himself (Dobkin de Rios and Janiger 2003). Also in 1949, LSD enters the United States, brought in by Dr. Max Rinkel after visiting Hofmann. Rinkel gives LSD to Dr. Robert W. Hyde of the Boston Psychopathic Hospital and then to over 100 patients, students and health professionals. Rinkel and Hyde present their LSD research to the *American Psychiatric Academy* in 1950 (Rinkel et al. 1952). Rinkel suggests LSD interferes with adrenaline and noradrenaline to produce psychosis; an idea supported by Dr. Daniel H. Funkenstein, who had proposed a pituitary-driven explanation for the modulation of fearful mental states (Funkenstein 1955). Classed as a psychotomimetic throughout the 1940s, LSD is linked to the neurophysiology of schizophrenia. But in the next decade it rises to prominence in the field of psychotherapy.

2.6 1950s

LSD and mescaline research contribute significantly to the development of the phenothiazines, with chlorpromazine first synthesised in 1950. The psychiatrist Daniel X Freedman, at the NIMH, is one of the first scientists to propose the link between LSD and serotonin (Freedman 1961). At St. Georges Hospital, London, in 1950, neuropsychiatrist John R. Smythies links mescaline with the catecholamine neurotransmitters and postulates an endogenous chemical cause for schizophrenia. In collaboration with chemist John Harley-Mason and British psychiatrist, Humphrey Osmond, he develops the *"Transmethylation Hypothesis for schizophrenia"* (Osmond and Smythies 1952). Smythies and Osmond then move to Saskatchewan, Canada, and working with LSD and psychiatrist, Abram Hoffer, develop the *"Adrenochrome Hypothesis"* (Hoffer et al. 1954).

But the psychotomimetic theory for LSD is essentially a phenomenological misnomer and does not persist for long. One of the hallmarks of psychosis; the lack of insight, is not represented in the psychedelic state – resulting in a radically different experience to that of chronic schizophrenia. Only if given LSD without

prior knowledge might it be considered similar to psychosis. Such activities are not common practice in medicine. But they are explored by the military as part of MK-ULTRA from 1953, which grossly violates personal liberty over the next two decades (Lee and Shlain 1992).

International LSD research begins in Poland and Iraq (Rostafinski 1950; Graham and Khalidi 1954). Whilst in 1951 Walter Frederking, already familiar with mescaline, hears about LSD from his colleague Ernst Jünger and gives it to 60 patients. He remarks that clinicians ought to take a high dose themselves to understand their patients experience with the drug (Frederking 1953). In the United Kingdom large-scale clinical LSD therapy begins through the work of Dr. Ronald Sandison at Powick Hospital, Gloucestershire: *"It was an immensely exciting time. We were looking for a new world. It's hard now to recapture the excitement of those years. During the decade or so after the war we were talking about the new Elizabethan age; everything seemed possible."* (Sandison and Sessa 2008). Sandison came across LSD serendipitously after visiting Sandoz in 1952 and gives the drug to patients who were stuck in traditional psychotherapy (Sandison et al. 1954). In 1955 he opens the world's first purpose-built facility for LSD therapy. It allows five patients to undergo LSD therapy simultaneously. The average maintenance dose is 150 mcg a week. Sandison also adminesters psilocybin but finds LSD more effective. In 1955, he speaks at the American Psychiatric Association conference, describing his "psycholytic" model.

Other UK centres including the Marlborough Day Hospital in London, where hundreds of patients are treated using a psychoanalytical model and low doses of LSD combined with methylphenidate for a wide range of disorders including *"migraine, writer's block, frigidity, sexual perversion, pathological gambling, immaturity, character disorder and psoriasis."* (Buckman and Ling 1963). Freudian therapist, Joyce Martin at the Marlborough Day Hospital, uses LSD to allegedly "treat" homosexuality and together with Pauline McCririck also develops the "Fusion Technique" with LSD (Martin 1962).

From 1956 Czech physician, Milan Hausner directs the largest and longest-running LSD therapy operation of all time, near Prague. Over 700 patients are treated with over 6000 psychedelic sessions, continuing behind the Iron Curtain long after LSD is banned in the West (Crockford 2007). Also in Prague, in 1956 neuroscientist George Roubicek uses high dose LSD with a stroboscope to synchronise the brain's electrical activity (Roubicek 1962). A newly qualified doctor, Stanislav Grof, undergoes a session as one of Roubicek's volunteers and goes on to become one of the leading figures in psychedelic therapy. Another pioneer of psychedelic therapy in Europe is the German psychiatrist Hanscarl Leuner, who conducts 1,300 individual sessions with LSD, mescaline and psilocybin on psychiatric patients and healthy volunteers between 1955 and 1960 (Leuner 1962).

Following on from their *Addrenochrome Hypothesis*, Osmond and Hoffer use LSD on patients with alcohol dependence. Combined with supportive psychotherapy they describe abstinence rates of up to ninety-percent, far surpassing other treatments for the condition before or since (Chwelos et al. 1959). But these and

other uncontrolled studies of the time (e.g., Smith 1958) also receive criticism in terms of their methodologies.

In the 1950s, Osmond gives LSD to Bill Wilson, the founder of Alcoholics Anonymous, who later says: *"It is a generally acknowledged fact in spiritual development that ego reduction makes the influx of God's grace possible. . .So I consider LSD to be of some value to some people, and practically no damage to anyone."* (Hartigan 2000). Osmond gives mescaline to the British writer Aldous Huxley in May 1953, who then writes, *The Doors of Perception* (Huxley 1954). In letters between them, Huxley and Osmond ponder what these drugs should be called; neither comfortable with the term "psychotomimetic." Huxley suggests *phanerothyme*, in a brief poem: *"To make this trivial world sublime, take half a gramme of phanerothyme,"* and Osmond's famously replies: *"To fathom hell or soar angelic, just take a pinch of psychedelic."* Osmond uses the term publicly at a meeting of the New York Academy of Sciences in 1957 (Osmond 1957) and popularisation soon follows.

By 1952 reports of LSD are emerging being used recreationally by physicians in Los Angeles. Psychedelics also infiltrate the Beat culture with Burroughs searching for ayahuasca in 1953 (Burroughs and Ginsberg 1963). In 1957, the banker Gordon Wasson takes psilocybin mushrooms with the Mazatec curandera Maria Sabina, and the subsequent publication in *Life* magazine propagates psychedelics widely (Wasson 1957). Psilocybin is subsequently extracted from mushrooms by Hofmann et al. (1958). By now, psychedelics are increasingly described as tools for spiritual enlightenment, with philosopher Alan Watts taking LSD in San Francisco, administered by Sterling Bunnell and Michael Argon in 1959. By the 1960s, the widespread recreational use of LSD starts the eventual downfall of its medical research.

2.7 1960s

In the 1960s, psychiatry embraces LSD for a wide range of problems, including the "neuroses" (anxiety disorders), depression, social anxiety in autism and pain relief – as well as some dubious diagnoses including female frigidity and homosexuality. A lot of research from this period – from the likes of Leary, Pahnke, Janiger, Barron, Barr, Lilly, Zegan, Harman and others – also explores many non-medical issues, including creativity, spirituality and personality types, and are not covered in this essay.

Mogar et al. give LSD to subjects between 6 and 10 years old with severe autism, that had failed to respond to other forms of treatment, and see consistently improved speech in these otherwise muted patients, greater emotional responsiveness to other children and adults, increased positive mood, smiling, laughter and decreased obsessive-compulsive behaviors (Mogar and Aldrich 1969). Mainstream acceptance is growing, with a number of important conferences. In 1960, delegates from seven European countries hear Sandison propose the term "psycholytic therapy" – meaning "mind-loosening" at the first "European Symposium on Psychotherapy under LSD-25" convened at Goettingen University under the auspices of Hanscarl Leuner,

who later forms the European Medical Society of Psycholytic Therapy in 1964 (Passie 1997). And a symposium is held in London in 1961 by the British Royal Medico-Psychological Association, "Hallucinogenic Drugs and Their Psychotherapeutic Use."

An important pioneer in exploring the role of psychedelics in treating trauma is the Dutch psychiatrist, Jan Bastiaans, who had experienced the German invasion of Holland and saw traumatised people returning from Auschwitz (Snelders 1998). He uses a combination of LSD, psilocybin, Sodium Pentothal, psychoanalysis and psychodrama to explore traumatised patients' experiences; one of whom is the Israeli writer Yehiel De-Nur, a survivor of Auschwitz and author of the book *Shivitti* (Zetnik 1989).

Chicago psychiatrist Eric Kast shows that LSD given at sub-psychedelic doses without formal psychotherapy out-performs traditional opiate-based drugs for relieving pain and anxiety for patients with end-stage cancer (Kast 1967). His work highlights the classical psychedelic drugs' effects on vasoconstriction that would be revisited 40 years later in contemporary research with cluster headaches. Kast's work is expanded by Grof, who in 1965 emigrates to the USA and becomes the chief of the Maryland Psychiatric Institute. Grof conducts hundreds of psychedelic-assisted sessions on cancer patients. Together with Joan Halifax he explores the existential experience of death (Grof et al. 1977) and also the drug DTP in patients with chronic alcohol dependency (Grof 1973).

Alcoholism is explored frequently with LSD with varying rates of success depending on the methodology of the studies. Uncontrolled studies using single high dose LSD find improved abstinence rates of between thirty and fifty percent (McLean et al. 1961; Kurland et al. 1967; Ditman and Bailey 1967 and Rydzynski et al. 1968). Controlled studies also have variable rates of success (Jensen and Ramsay 1963). Some researchers are skeptical of the claims of early researchers and find no significant differences in drinking habits between the groups (Smart et al. 1966). One study interviews the wives of men who had received LSD-assisted treatment compared to the wives of men who had received standard treatment for alcoholism. Both groups report improvements in their husbands (Sarett et al. 1966). Another study looks at female alcoholics (Van Dusen et al. 1967) and one compares high dose LSD with dextroamphetamine and finds no differences (Hollister et al. 1969). Other studies compare LSD with traditional treatments for alcoholism and find no significant difference in drinking habits and employment between the groups (Johnson 1969; Bowen et al. 1970) or a lack of lasting improvements (Kurland et al. 1971; Faillace et al. 1970). Further criticism of LSD therapies for alcoholism comes from a large study published in 1970 revealing no significant differences in abstinent rates between the groups at three, six, nine and 12 months (Ludwig et al. 1970). However, this study also attracts criticism for failure to adequately address set and setting.

In the 1960s, psychedelics provide innovative doctors an opportunity to challenge the prevailing medical and social models. The Scottish psychiatrist, R.D. Laing, who had risen to fame with his influential book, *The Divided Self* (Laing 1963), advises any would-be psychoanalysts to: "*Number One, read the works of Freud. Number*

two, undergo a personal analysis and number three, take LSD" (Laing 1997). In 1965, he starts an experiment in psychiatric communal living in which patients and doctors live side by side at Kingsley Hall in East London. Treatments with LSD and other psychedelics are commonplace, the guiding principle being "*to break down is to break through*." Laing enjoys his celebrity status and treats many patients from the London glitterati (Zeal, 2010, personal communication).

As the recreational use of psychedelics increases – particularly after LSD is banned – increasing cases of LSD-induced psychosis appear (Blumenfield and Glickman 1967; Ungerleider et al. 1966; Smart and Bateman 1967). However, large meta-analyses at the time demonstrate a low incidence of adverse reactions. Over 2000 papers on the therapeutic uses of LSD between 1950 and 1966 show that despite being used generally on the most treatment-resistant cases, when prescribed judiciously in the clinical setting, LSD is overwhelmingly safe and effective. A review of studies from the 1950s that includes 5000 subjects and 25,000 drug sessions find rates of psychosis of only 0.2 % and suicide of 0.04 % (Cohen 1960). Another review of 700 psychedelic drug sessions describes only one psychosis (Chandler and Hartman 1960), and an analysis of UK psychedelic therapies of 350 patients over 4 years finds only one attempted suicide (Ling and Buckman 1963). A large meta-analysis at the end of the 1960s of over 4000 patients and 50,000 psychedelic sessions, mainly with LSD, identifies only two completed suicides and thirty-seven patients with a prolonged psychosis. Thus concluding: *"Treatment with LSD is not without acute adverse reactions, but given adequate psychiatric supervision and proper conditions for its administration, the incidence of such reactions is not great."* (Malleson 1971).

An important figure in early American LSD research is psychiatrist Sidney Cohen of the Veterans Administration Hospital in Los Angeles. He is also Professor of Medicine at UCLA and editor of the Journal of Psychopharmacology. Together with Betty Eisner, Cohen conducts LSD sessions exploring a wide range of diagnoses including depression, anxiety, schizophrenia and alcohol dependency (Cohen et al. 1958; Cohen and Eisner 1959). Eisner later serves on the board of the Albert Hofmann Foundation, pioneering the concept of the male–female co-therapist pair for delivering sessions (Eisner and Cohen 1958). Cohen later directs the Division of Narcotic Addiction and Drug Abuse and describes the potential harms of recreational use, collating his publications in the volume *The Beyond Within* (Cohen 1965). As a footnote, when Laura Huxley injects her husband on his deathbed with 100 micrograms of LSD it is Cohen who supplies the drug (Huxley 1968).

In 1966, LSD is banned, having leaked from the medical community and being widely used recreationally. Sandoz stops producing *Delysid* and within years virtually all medical research had halted. A plethora of reports follows, suggesting LSD causes chromosomal damage (Cohen et al. 1967; Dishotsky et al. 1971), which is subsequently disputed (Grof 1980). But the damage is done and the negative press paid to psychedelics is to seriously hamper research for the next 30 years.

2.8 1970–1975

Superficially the 1970s and 80s are the dark ages for psychedelic medicine. Nixon's "War On Drugs" limits doctors prepared to stand up against global governments' anti-psychedelic rhetoric (Dahlberg et al. 1968). Meanwhile, research proposes links between schizophrenia and LSD use (Breakey et al. 1974). But the lack of phenomenological and epidemiological correlations (Snyder et al. 1974) and the greater role played by non-psychedelic drugs (McLellan et al. 1979), particularly the potent dopamine agonists, cocaine and amphetamine, are recognised as more likely candidates as a cause for psychosis (Angrist et al. 1974). In the 1970s legal LSD becomes difficult to obtain. Some clinicians are permitted to keep using it until their supplies ran out. In the UK, this continues until the middle of the 1970s (Sessa 2010). But behind the Iron Curtain, away from the West's struggle with its developing drug culture, LSD research continues – especially in Czechoslovakia under Milan Hausner.

Despite the problems, it is recognised that LSD and mescaline research innovatively spearheaded neuroscience and hugely influenced the future of pharmacotherapies for mental disorders. Psychiatry was stuck in the nineteenth century before LSD; with only Freudian paradigms as its major clinical tool and only psychosurgery, insulin coma therapy and ECT as crude biological methods. Psychedelics changed all that. But the recreational use of drugs and the ensuing social upheaval prompts successive governments to clean up what they see as the mess created by LSD. Decades of positive work with psychedelics is effectively discounted. The general public – and a whole generation of doctors – are taught only of the exaggerated dangers of psychedelics, with no mention of the important role these drugs had played in the development of modern psychiatry. By the end of the 1970s, for most people, LSD is nothing but an old-fashioned mistake from the past.

2.9 1975–1980

But the 1970s are not quite such dark after all. Outside of medicine underground culture continues. Some choose to live communal lives beyond society and illicit LSD production and distribution flourishes (Roberts 2008; Fielding 2011). Many psychedelic researchers of the 1950s and 60s, disheartened by government restrictions, leave the field. But small pockets of interest continue. Some meet to discuss and integrate the past, turning their attention to the study of shamanic practices. In 1978, the *International Transpersonal Association* is formed, with Stan Grof as President, together with Michael Murphy and Richard Price – the founders of California's Esalen Institute (Grof et al. 2008). Having grown out of the Transpersonal Movement of the 1960s, it is a natural progression to emerge in the wake of the restrictions put on LSD therapy (Freeman 2006). Unable to openly use LSD for psychotherapy, Grof and his wife Christina develop the practice of Holotropic Breathwork© and start offering classes in 1976. The technique involves "moving toward wholeness," using breathing and other physical and psychological elements for self-exploration and becomes widely used throughout the world (Eyerman 2013).

Some psychedelic therapists continue to practice underground and others explore other, still legal, compounds. The Jungian psychotherapist, Leo Zeff, who had used LSD in his Californian practice until it was banned in 1966, is introduced to MDMA in 1976 by chemist, Alexander "Sasha" Shulgin, who had been synthesizing psychedelics since the early 1960s (Shulgin 1964). Shulgin calls MDMA his "low-cal Martini" and together with chemist, David E. Nichols, publishes the first report into the psychoactivity of MDMA in humans (Shulgin and Nichols 1978). Not a "classical" psychedelic, but rather an "entactogen" (a term coined by Nichols), MDMA produces a gentler, more euphoric state than LSD. It seems the perfect drug for post-trauma psychotherapy; shorter-acting and therefore more clinically manageable, MDMA increases feelings of empathy and bonding, as well as relieving depression and allowing users to access and process memories of emotional trauma (Sessa 2012). Zeff recognises its therapeutic potential, stating it "stripped away neuroses and put users in a primordial state" (Brown 2002), and throughout the late 1970s and into the 1980s he uses it on hundreds of patients (Stolaroff 1997).

Another practitioner, Mylon Stolaroff, who in the 1960s had administered LSD and mescaline to over 350 participants and explored the role of psychedelics to assist creativity (Harman et al. 1966), moves onto other substances in the 1970s. Having founded the *International Foundation for Advanced Study* in California, throughout the 1970s and into the 1980s he continues providing psychedelic therapy with unscheduled compounds; describing hundreds of sessions with MDMA and other newly emerging experimental drugs (Stolaroff 1994). New compounds emerge from Alexander Shulgin's laboratory, such as 2C-B, 2C-E, 2C-T-7, 2C-T-2 and DOM. Shulgin, together with a selected closed group including his wife, the psychotherapist Ann Shulgin, carry out self-testing and meticulous documentation of the compounds as they are produced (Shulgin and Shulgin 1991, 1997).

2.10 1980s

Psychotherapists in the early 1980s using MDMA, which was initially called "Empathy," are keen to keep it within the clinical community. But MDMA's growing popularity is impossible to hide. Rebranded as the more marketable "Ecstasy," MDMA spreads. Popular in the Starck Club, Dallas, it is distributed widely as a "yuppie psychedelic" under the brand name "Sassyfras" and soon becomes known in the wider American public with further exposure on television (Eisner 1989).

In 1984, the DEA announces that it intends to make MDMA a Schedule One drug, prompting a response by the clinical research community, including Thomas Roberts, Lester Grinspoon, James Bakalar and George Greer. They request a hearing to debate the DEA's intention. In 1985, a small gathering meet at the Esalen Institute, co-sponsored by Rick Doblin of the Earth Metabolic Design Laboratories. Psychiatrists Joseph Downing and Phillip Wolfson describe their successful use of MDMA to their patients. Thirteen of the conference participants take MDMA experimentally under supervision as part of the event (Greer 1985). Psychiatrist Rick Ingrasci, having conducted 150 MDMA sessions with 100 patients with overwhelmingly

positive results, testifies in favour of continued MDMA research. (Ingrasci 1985). Nevertheless, in May 1985 the DEA places MDMA in an emergency Schedule One category for a one-year period pending further investigations, prompting Doblin to form *The Multidisciplinary Association for Psychedelic Studies*, *MAPS*.

The first major MDMA Conference is held in 1986 in Oakland, California. Speakers include George Greer, David Nichols Alexander Shulgin and Frank Sapienza from the DEA (Seymour and Wesson 1986). Greer, together with his wife and psychiatric nurse co-therapist, Requa Tolbert, publish a series of uncontrolled case studies describing the use of MDMA with couples or in groups, conducted before the ban (Greer and Tolbert 1986). The role of MDMA as a tool for increasing sexual intimacy is well known by therapists (Buffum and Moser 1986) and the drug is also being used to attain sexual and spiritual ecstasy by followers of the popular Western guru, "Osho," Bhagwan Shree Rajneesh. In the late 80s, followers of Osho spread to India and to the Balearic island of Ibiza, spawning the subsequent development of the rave scene (Coutinho 2006).

In 1988, Dr. Evgeny Krupitsky and colleagues at the Leningrad Regional Center for Alcoholism and Drug Addiction Therapy begin investigating Ketamine in the treatment of alcohol and heroin addiction (Krupitsky and Grinenko 1997; Mash et al. 1998). Ketamine, an anaesthetic in low doses, induces a profound psychedelic experience with recognised anti-craving properties similar to the other NMDA-receptor antagonists acamprosate and ibogaine (Bowdle et al. 1998). It is also short acting and not a scheduled drug, so more easily approved for off-license research.

The Swiss Federal Office for Public Health grant permission in 1988 for the *Swiss Medical Society for Psycholytic Therapy* to conduct individual and group psychotherapy with MDMA and LSD. Over a hundred patients with a wide range of psychiatric problems receive an average of eight psychedelic sessions. After nineteen-months follow-up over ninety-percent of patients have experienced good or slight improvements (Gasser 1995). But in the wake of growing recreational ecstasy use the project is terminated in 1993. In the USA, in 1988, New Mexico psychiatrist, Dr. Rick Strassman, begins planning a human research study using the classical psychedelic drug dimethyltryptamine (DMT). This signals the beginning of a new chapter in human psychedelic drug research.

2.11 1990s

In December 1990, Strassman starts his DMT pilot study on healthy volunteers to establish intravenous dosage, safety parameters and physiological measures. The project re-launches psychedelic medical research with humans, demonstrating that regulatory authorities can be persuaded to consider psychedelics again (Strassman 2001).

Following a two-year follow-up, Greer and Tolbert publish the outcomes of eighty patients treated with MDMA Psychotherapy (Greer and Tolbert 1990). But now rave parties have emerged from their niche beginnings into massive large-scale events, and several high profile deaths of young people prompt crackdowns. In 1992,

Professor of Child and Adolescent Psychiatry at UCLA, Charles Grob, submits a proposal to use MDMA-assisted psychotherapy on patients with anxiety secondary to end-stage cancer and begins a physiological Phase One study (Grob et al. 1996). But efforts to obtain approval for the clinical study are rejected twice by the FDA, leading Grob to use psilocybin instead of MDMA.

The following year a group of psychiatrists, pharmacologists and chemists, David Nichols, George Greer, Mark Geyer, Dennis McKenna, Phil Wolfson and Charles Grob form the *Heffter Research Institute*. Named after the nineteenth century pharmacologist, Arthur Heffter, the group dedicate themselves primarily to the study of the classical psychedelics. Throughout the early 1990s, Nichols and Shulgin produce and test many new products for development by their psychiatric colleagues. And in 1993, Stolaroff publishes preliminary results of psychotherapy with 2C-T-2 and 2C-T-7 as possible therapeutic alternatives to MDMA (Stolaroff and Wells 1993).

Inconsistences develop between the clinical MDMA community who propose the drug is safe in controlled circumstances, and the media and politicians who favour strict prohibition to control recreational use. In 1995, it transpires that a widely publicised anti-ecstasy campaign in the UK has actually been sponsored primarily by the brewing industry, whose business is being eroded by ecstasy use (Carey 1997). Other psychedelics with clinical potential are also appearing. In 1992, Jan Bastiaans begins working with Howard Lotsof who had been addicted to heroin since the age of 19-years before he discovered the anti-addictive effects of ibogaine (Lotsof 1995). However, in 1994, a patient dies during the course of an ibogaine session and Bastiaans, accused of neglect, has to end his clinical practice (Snelders 1998).

Strassman's DMT study is published in 1996 (Strassman 1996). And in 1998 Franz X. Vollenweider founds the Zurich branch of the *Heffter Research Institute*, which publishes over 80 peer-reviewed papers providing invaluable non-clinical physiological and mechanistic research for psychedelic studies (Liechti et al. 2001a; Vollenweider 2002; Vollenweider et al. 2002). Another breakthrough comes at the University of Arizona with a case study describing a 34-year-old man who finds relief from Obsessive-Compulsive symptoms after eating psilocybin mushrooms (Moreno and Delgado 1997). With support from both, the Heffter Research Institute and MAPS, Delgado and Moreno plan a human clinical study with psilocybin for OCD.

In the UK, 1998 sees the formation of the *Beckley Foundation*, a charitable organisation focusing on drug policy and scientific research. The director, Amanda Feilding, forms a research affiliation with Professor David Nutt, psychopharmacologist at Bristol University. By the end of the decade, the use of the South American DMT brew ayahuasca is making inroads into Europe. Barcelona's Jordi Riba gains approval for a ayahuasca study on healthy volunteers (Riba 1998). More people are reaching out in creative ways to alter their consciousness and a whole generation of psychedelic enthusiasts from the 1960s steps out of the shadows to provide the cultural roots.

2.12 2000s

Notable geographical centres spearheading psychedelic research emerge, including Johns Hopkins University, the University of New Mexico, McLean Hospital in Harvard, Imperial College London and Bristol University in the UK. Dispute around the potential neurotoxic effects of ecstasy continue, especially for heavy and frequent users. In a study comparing ecstasy users, non-users and cannabis users, the heavy users (with an average lifetime use of 120 tablets) score worse in verbal short-term memory and executive function tasks (Gouzoulis-Mayfrank et al. 2000). But confounding factors and political opinions colour the debate. Many of the early studies of the 2000s focus on "recreational ecstasy users," though confounding factors (particularly cannabis use) give a false impression of risks (Morgan 2000). And in 2001 a study with direct relevance to planning clinical studies with MDMA looks at gender difference reactions to MDMA; with women being more sensitive than men, suggesting that MDMA therapists take gender into account (Liechti et al. 2001b).

In the early 2000s, the risk of MDMA causing hyperthermia, hyponatreamia and liver toxicity all receive attention. But the neurotoxicity debate dominates the scientific and popular literature. In 2002, Dr George Ricaurte publishes a study in the journal *Science* apparently demonstrating severe neurotoxicity in primates with only moderate amounts of MDMA (Ricaurte et al. 2002). The study is highly influential and sensationalist pictures of brains with holes appear on television, stating clear justification for restrictions on MDMA research. But then, in 2003, it transpires Ricaurte's team had not given their primates MDMA after all, but rather the highly toxic methamphetamine. The study is subsequently retracted from *Science* (Ricaurte et al. 2003), but public concern of MDMA remains high. Nevertheless, by now, more than one million people in the UK have used ecstasy recreationally at a rate of 30 million doses a year and mortality and morbidity statistics remain low compared to other drugs. A study in 2003 demonstrates that after removing confounding factors of concomitant drugs there are only three deaths per year from 1997 to 2000 attributed solely to MDMA (Schifano et al. 2003). In support of this, John Halpern at Harvard looks at a population of Mormons who used only MDMA with no other drugs, including alcohol and shows no evidence of neurotoxicity (Halpern et al. 2004). Further studies demonstrate that infrequent sessions with MDMA produce no lasting neurotoxicity or neurocognitive impairments (Ludewig et al. 2003).

Undeterred by the political challenges, MAPS and Heffter continue to support psychedelic research wherever they can. In Spain, in 2000, Dr. Jose Carlos Bouso gets approval for a MAPS-sponsored study looking at MDMA for PTSD. But after 1 year, having dosed just 6 of the planned 29 patients, a political backlash by the Spanish government shuts down the study. Also in 2000, Rick Doblin meets South Carolina psychiatrist, Michael Mithoefer, at an ayahuasca conference in San Francisco sponsored by legendary psychedelic therapist, Ralph Metzner. They plan a randomised placebo-controlled study for PTSD with MDMA-assisted psychotherapy. And in the early years of the 2000s, Riba and colleagues publish further physiological studies on ayahuasca (Riba et al. 2001, 2002; Riba 2003).

In the UK, the first editorial since the 1960s on psychedelic medicine appears in the British medical press, a symposium on psychedelics is held at the Royal College of Psychiatrists and Ronnie Sandison, now in his eighties, comes out of a retirement in defence of psychedelic therapy (Sessa 2005, 2006). The psychedelic research community celebrates Albert Hofmann's 100th birthday with a major conference in Basel in 2006. As Albert makes his way across the stage to accept a bouquet of red roses he jokes to the audience, "Sorry about the walking stick – I have to keep reminding myself I am no longer in my nineties!" And from McLean Hospital, Harvard, a study interviews 53 cluster headache patients and describes how sub-psychedelic doses of psilocybin or LSD diminishes the frequency and severity of attacks (Sewell et al. 2006).

During an anesthetics study in 2006 on complex regional pain syndrome (CRPS), with no psychedelic research intentions, it is discovered that Ketamine reduces depressive symptoms (Correll and Futter 2006). A further small study confirms the result (Khamsi 2006) and a larger study in Oxford gets underway (McShane, 2013, personal communication), heralding a radical new way of developing treatments for depression. In 2006, Moreno and Delgado publish their psilocybin OCD study, showing the drug is well tolerated and causes impressive reductions in obsessive-compulsive symptoms (Moreno et al. 2006). The same year, a team at Johns Hopkins University, lead by Roland Griffiths, veteran psychedelic researcher William Richards and Jesse Roberts of the Council of Spiritual Practice, describes its exploration of psilocybin as mystical agent (Griffiths et al. 2006).

In 2007, Kevin Balktick and Neal Goldsmith launch *"Horizons: Perspective of Psychedelics"* conference in New York. And in the UK, under the auspices of the Beckley Foundation and Professor David Nutt, Robin Carhart-Harris and Ben Sessa start the UK's first human psychedelic study, which becomes a precursor for an fMRI study.

In 2008, the Johns Hopkins team publish the two-year follow-up to their study of mystical experience, describing lasting positive personality changes, signaling profound implications for the treatment of Personality Disorder (Griffiths et al. 2008). Keen to see research with LSD resume again in Hofmann's lifetime, the Swiss psychotherapist Peter Gasser designs a double-blind study, sponsored by MAPS, for the treatment of anxiety for patients with end-stage cancer (Gasser 1995). Hofmann pronounces, *"My wish has come true. I didn't think I'd live to find out that LSD had finally taken its place in medicine."* A second major research conference occurs in Basel in 2008 and Albert Hofmann dies soon afterwards, aged 102 years old. This same year saw the publication of a book by Henrik Jungaberle, Peter Gasser, Jan Weinhold and Rolf Verres: "Therapy with psychoactive substances. Practice and critique of psychotherapy with LSD, psilocybin and MDMA" (Jungaberle et al. (2008)). It became a highly influential and widely read text documenting historical and contemporary psychedelic therapies, in particular the work carried out between 1988 and 1993 by the *Swiss Medical Society for Psycholytic Therapy* exploring individual and group psychotherapy with psychedelics. Providing qualitative analyses of their therapeutic practices, differences in approach and ethics the book was complemented by contributions from psychedelic

researchers and practitioners like Stan Grof, Grob and Franz Vollenweider. It has since been a reference point for the renaissance of psychedelic therapy research in Germany.

In the UK in 2009, the Royal College of Psychiatrists hosts another psychedelic symposium, inviting Mithoefer and Grob. The message is that moderate and infrequent doses of MDMA on screened patients in a controlled setting poses no demonstrable risk to health. Furthermore, if neurophysiological changes do occur they appear to be reversible with a year's abstinence from the drug (Selvaraj et al. 2009). Despite these advances a negative political agenda continues to restrict medical research (Sessa and Nutt 2007). In 2007, a review in *The Lancet* criticises current drug classification and declares the present system unfit for purpose in relation to MDMA and LSD; stating current laws give the wrong message to the public and hamper research on psychedelics (Nutt et al. 2007). The Advisory Committee on the Misuse of Drugs (ACMD), chaired by Nutt, prepares a report about ecstasy for the British government requesting MDMA be moved to Class B, better reflecting its relative safety (Home Office 2009). But the UK government disregards the ACMD's advice. Objecting to this neglect of expert opinion, Nutt protests in the scientific and popular press and is sacked from the ACMD. He subsequently forms the Independent Scientific Committee on Drugs (ISCD) to campaign for a non-political approach to pharmacology research. That year, Dr. Sessa becomes the first person in UK to be legally administered psychedelics since the 1970s when he is injected with psilocybin by Nutt (Carhart-Harris et al. 2010).

In 2009, German psychiatrist, Friederike Meckel and her husband Konrad Fischer, describe their use of underground psychotherapy in Switzerland. The couple were briefly imprisoned for their practice with MDMA, LSD and 2C-B. The qualitative reports of success with their patients were strongly in favour of the benefits of psychedelic drug-assisted psychotherapy and the incident sheds light on the previously unknown scale of underground therapy in Europe (Sessa and Meckel Fischer 2015). That same year, Dr. Steve Ross, Addictions Psychiatrist at New York University, begins enrolling for a double-blind, placebo-controlled pilot study to assess the efficacy of psilocybin on anxiety associated with advanced cancer.

2.13 Since 2010

A golden year for publications in the field, 2010 sees Grob showcase his psilocybin cancer study (Grob et al. 2010) and Mithoefer publish his MDMA proof-of-concept study (Mithoefer et al. 2010), showing that 80 % of the MDMA-treated PTSD group experienced clinical benefit, against twenty percent of the placebo group. Also in 2010, Swiss psychiatrist Peter Oehen, finishes the experimental sessions with MDMA in twelve treatment-resistant PTSD patients. Easter 2010 sees MAPS, together with the Heffter Institute, the Council of Spiritual Practices (CSP) and the Beckley Foundation host a large international conference in San Jose, USA.

In April 2011, *Breaking Convention*, the UK's first multidisciplinary conference dedicated solely to psychedelic research, founded by Ben Sessa, David King, David Luke, Cameron Adams and Anna Waldstein, takes place at Kent University in Canterbury. In the same year, Torsten Passie and John Halpern, publish a widely read book on the psychopharmacology of LSD (Passie et al. 2008).

The Imperial College team showcases an fMRI study of intravenous psilocybin (Carhart-Harris et al. 2012a, b) and validate their results with MEG scanning (Muthukumaraswamy et al. 2013). A large grant follows, kick-starting an investigation into psilocybin-assisted psychotherapy for treatment-resistant depression (Carhart-Harris et al. 2016b). That same year, Norwegians Krebs and Johansen publish a meta-analysis reviewing six randomized trials of LSD-for-alcoholism from the 50s and 60s. Taken together, these early studies describe favourable results, demonstrating a strong case for revisiting psychedelic research for addictions (Krebs and Johansen 2012). Also in 2012, Michael Bogenschutz at the University of New Mexico publishes a review of psychedelic therapy for addictions and begins the first addictions study with psilocybin since the 1970s (Bogenschutz and Pommy 2012). Matthew Johnson at Johns Hopkins starts his small pilot study using psilocybin therapy for nicotine addiction. And the results of Oehen's Swiss MDMA study demonstrate substantial improvements for treatment-resistant PTSD (Oehen et al. 2012; Chabrol and Oehen 2013). Mithoefer publishes his four-year follow-up study showing maintained remission with no further doses of MDMA since the original therapy (Mithoefer et al. 2013).

Planning begins for the Cardiff MDMA Project in 2013, using fMRI to study MDMA in combat-PTSD sufferers. In the same year Doblin and Mithoefer attend a meeting at the Pentagon to discuss possible funding for MDMA-PTSD by the US military. In Oakland, California, the Psychedelic Science conference is held, organised by MAPS in affiliation with Heffter, Beckley and the CSP. July 2013 sees the approval of an MDMA-Assisted Therapy for the treatment of social anxiety in autistic adults by Charles Grob and Alicia Danforth. The same month in London, *Breaking Convention*'s second gathering hosts 850 speakers and delegates from thirty-nine countries. And psychedelics take a step into mainstream awareness with a paper describing a large sample of recreational users for whom psychedelics have had a positive effect on their mental health (Krebs and Johansen 2013).

The community mourns the loss of Sasha Shulgin in 2014. The *Journal of Psychoactive Drugs* publishes a special issue titled *Psychedelic Resurgence—Research and Therapeutic Uses, Past and Present,* with articles from contemporary and historical researchers (Chambers 2014; Smith et al. 2014; Winkler and Csémy 2014; Nichols 2014; Emerson et al. 2014; Parrott 2014; Cole 2014; Loizaga-Velder and Verres 2014; Greer et al. 2014; Sessa 2014). By now it is clear MDMA adequately satisfies the risk-benefit analysis for clinical use (Doblin et al. 2014). In the field of addictions psychedelic therapies progress with the publication of psilocybin studies for nicotine (Johnson et al. 2014) and alcoholism (Bogenschutz et al. 2015).

Shulgin's influence is honoured in 2015 by a special edition of the *British Journal of Psychiatry*, featuring a painting and commentary by visionary artist Alex Grey on the cover (Sessa and Grey 2015) and articles on addictions (Sessa and Johnson 2015)

and politics (Sessa and Nutt 2015). *Breaking Convention* hold their third meeting in summer 2015 in London amidst continued positive media influences. Mainstream journals are now increasingly dedicating entire issues and encouraging pieces on the subject (Sessa 2015).

As we progress through 2016, the studies, conferences and articles continue to roll in faster than they can be summarised. Imperial College subject LSD to the same neurophysiological studies with fMRI and MEG as with psilocybin before and publish to wide critical acclaim (Carhart-Harris et al. 2016a). Further studies reveal how music influences the experience (Kaelen et al. 2015, 2016) and how personality changes result from psychedelic use (Lebedev et al. 2016). New UK studies are planned for MDMA and alcoholism, whilst LSD micro-dosing for cognitive impairment and enhancing creativity are completed (Raz, 2016, personal communication).

3 Conclusions

Psychedelics have taken a torturous path through medicine; resolving early issues of set and setting, mimicry versus cause of psychosis, arguments about toxicity and regulatory challenges. The socio-political climate changed significantly in the late 1980s. And now, in the twenty first century, psychedelic research is well established again. But this time the medical profession's slant is different. There is less novelty about cultural psychedelia and less emphasis on changing the world. Today, the general public understand drugs far better than in the 1960s. They recognise that it is methamphetamine, crack and alcohol that cause dependence and destruction, whereas that drugs like LSD, psilocybin, cannabis and MDMA can be used safely. They are simply too pharmacology savvy to fall for the blanket and unsophisticated "Just Say No." Together with tremendous advances in neuroimaging, providing visualisation not only of the anatomical structure of the brain but also its direct physiological changes in real time, psychedelics have become the ideal tools for a bespoke approach to neuroscience. In the dying embers of the War On Drugs, the therapeutic validity of psychedelics is impossible to ignore.

Global institutions are working in harmony towards a shared goal. But there remain challenges. There is little support from the pharmaceutical industry; perhaps unsurprising given that psychedelic treatments use drugs that are out of patent. Plus, psychedelic therapy is the antithesis of the traditional maintenance therapies we use in modern psychiatry. Through focusing on objective scientific data neuroscientific studies raise the profile of contemporary research and pull in greater mainstream acceptance for the field. Meanwhile, cross-cultural studies are teaching us about the holistic management of mental disorders. The concepts of Mindfulness and Wholeness are now commonplace in psychiatry; broadening our minds as to what we consider "psychedelic."

Psychiatry today is where nineteenth century general medicine was before the discovery of antibiotics; expert at the identification and classification of common disorders but lacking globally agreed treatments. It could be that psychedelic therapies, however, can offer psychiatry the best opportunity to effectively tackle

trauma using guided psychotherapeutic techniques; driven by a holistic, naturalistic and personalised care approach that is currently lacking. Psychedelic psychiatry is in desperate need of good PR if it is to realistically meet modern demands and become clinically deliverable for large populations. This is our challenge for the future. Given the pace of recent clinical research, we are clearly in the midst of a psychedelic renaissance and the best is yet to come. Watch this space.

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