The History of Psychedelics in Psychiatry

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ABSTRACT

Initial interest in the value of psychedelic drugs ("psychotomimetics") in psychiatry began in the early 20th century, with explorations of the possibility that mescaline or peyote could produce psychosis-like effects. Over time, interest was focused on whether the effects of psychedelics could inform as to the underlying basis for psychiatric disorders. As research continued, and especially after the discovery of LSD in 1943, increasing interest in a role for psychedelics as adjuncts to psychotherapy began to evolve and became the major focus of work with psychedelics up to the present day.

Introduction

Until the 1950s, there was generally little thought given to the role of neurochemistry in mental disorders. The age of biological psychiatry only started following the discovery of LSD and with the introduction of chlorpromazine, reserpine, and monoamine oxidase inhibitors.

Initial interest in the value of psychedelic drugs sprung from the possibility that they might produce mental effects like those of schizophrenia or other psychiatric disorders. Therefore, these substances were called psychotomimetics (meaning psychosis-mimicking) or hallucinogens (producing hallucinations). In recent years, psychedelics has become the preferred name, which connotes that these substances manifest properties of the mind. The term includes all substances that have an agonist or partial agonist effect at brain serotonin 5-HT_{2A} receptors, such as LSD, mescaline, or psilocybin.

Early studies with peyote and its active component mescaline simply characterized the nature of their effects on the psyche. Over time, more interest was focused on whether the effects of psychedelics resembling mental illnesses could inform as to the underlying basis for psychiatric disorders. As investigations continued, a role for psychedelics as adjuncts to psychotherapy began to evolve and became the major focus of work with psychedelics up through the present day.

After the discovery of LSD in 1943 and its rather widespread availability, numerous studies were directed toward treatment of alcoholism and addiction. Within the space of a few years, the published literature on the potential medical value of psychedelics grew enormously, so as today it is virtually impossible to keep count of the plethora of publications in this field. According to Dyck [1], "LSD trials represented a fruitful, and indeed encouraging, branch of psychiatric research occurring alongside more famous and successful trials of the first generation of psychopharmacological agents…" "By 1951, more than 100 articles on LSD had appeared in medical journals, and by 1961, the number increased to more than 1,000 articles" [1].

The idea that drugs produce "artificial psychoses" was already prominent in early 19th century medical theory, but it was the German psychiatrist Emil Kraepelin, who began as one of the first investigators to explore the phenomena of mental illness on a scientific basis, using "experimentally induced psychoses". Kraepelin believed the origin of psychiatric disease to lie in biological and genetic malfunction. That was the main incentive for him and his pu-

pils to establish experimental methods to investigate the action of tea, alcohol, morphine, and other drugs on mental processes.

Kraepelin argued that psychiatric questions should be investigated by observation and experimentation as in other natural sciences. His theories were dominant at the start of the 20th century but were largely ignored in the face of the later psychodynamic influence of Freud and his disciples in the United States. But Kraepelin's ideas enjoyed a revival in the last half of the 20th century and laid the foundation of the modern classification system for mental disorders [2].

Attempts to Model Mental Illness with Mescaline

Knauer and Maloney [3], working in Kraepelin's clinic, noted that none of the drugs that had been studied earlier by Kraepelin could be expected to model a psychosis, and decided to study mescaline in an attempt to produce mental conditions similar to types of "insanity". They experimented on themselves and on volunteers by subcutaneously injecting a solution of mescaline sulfate. They largely described qualitative aspects of the visual phenomena produced, but also noted dramatic effects on time perception.

In 1923, Kurt Beringer [4] proposed the use of mescaline to induce an experimental psychosis. In the subsequent years, several investigators carried out experiments to characterize the effects of mescaline in humans. Although some of those investigations attempted to draw parallels between certain of the effects of mescaline and aspects of mental illness, more often they were qualitative reports with little apparent relevance to mental illness. The doses of mescaline typically used were often rather low and sometimes did not produce any kind of effect.

In the same year, Fernberger [5] described a personal experiment where he ingested 39 g of dried peyote buttons. The direct result was an increased awareness of kinesthetic sensations, which was evident in many sensory modalities. He characterized his state as a "supernormally clear focus of attention" but with a rapidly changing focus. Now he was able to perceive stimuli that were normally well above the sensory threshold. Sensations appeared to be greatly enhanced in clearness but not in intensity. Whereas previous reports about mescaline had emphasized intense colorful visions, Fernberger experienced only slight visual effects and some colored visual manifestations. He did, however, perceive a distortion of space and time. Speech appeared to be slow and walking also became a "ponderous affair".

In 1927, Rouier [6, 7] published a comprehensive monograph of all the existing literature on peyote. He included comments about some of the previously published observations of "mescal intoxication," as well as 4 original observations. They were qualitative and chiefly described visual phenomena, generally typical of "mescal visions". The psychological aspects of peyote intoxication are least well treated, and American work in the field was largely ignored.

In 1932, Fernberger [8] cited work by a colleague who was studying the peyote cult with the Delaware Indians and had made several psychological observations. Some Indians emphasized that it had become socially admirable to suppress the peyote visions and, after some practice, that could be successfully accomplished. Fernberger conducted experiments with faculty members from the University of Pennsylvania to experience a peyote intoxication in a group setting designed to more nearly reproduce the situation in peyote ceremonies. The peyote buttons were prepared "in the Indian way" by boiling in water for about 1½ hours, and both the buttons and 1 or 2 cups infusion were ingested. The "meeting" was provided with drums and rattles, and, during the latent period, the participants spent their time playing them and learning songs of the Indian ceremony.

All experienced dilation of the pupils, marked exhilaration, and the lowering of social inhibitions, as well as enhanced visual and auditory sensory fields and a split personality sensation. Five subjects noticed a marked slowing of time, and 8 of 9 also experienced visual phenomena [5].

Four years later, Guttmann and Maclay [9] suggested small doses of mescaline as a therapy for derealization and personalization, due to the known symptoms of depersonalization during mescaline intoxication. But the symptoms that attracted the main interest of different researchers were the visual hallucinations and disturbances of sensory perception. Corresponding investigations led to the idea of making psychotherapeutic use of the different stages of mescaline intoxication.

In the same year, Guttman [10] published a paper, based on observations of 60 "mostly normal" subjects, following administration of 100–400 mg of synthetic mescaline sulfate. At that time, mescaline was already thought to induce psychosis-like phenomena without immediate risk or deleterious after-effects. Symptoms included changes in mood and sensory perception, disturbances of thought and in the visual sphere, impairment of tactile perception, hypersensitivity to noises, alteration of the perception of movement and of one's body, change in the perception of space and time, synesthesias, and various hallucinations. Several participants experienced suspicions that could develop into paranoid delusions. The variety of psychopathological symptoms that could be induced by this drug led Guttmann to the conclusion: "There is reason to suppose that patients in such a state may be very susceptible to psychotherapeutic influence".

Guttman considered that studies like these could teach something of general importance for psychiatry. He summarized his findings as follows: "(a) A new aspect of disintegration of sensory function, namely in the direction towards synesthesia. (b) A new idea of the importance of the perceptual sector within the personality, (c) Some therapeutic prospects, especially with regard to depersonalization states, and (d) An opportunity of experiencing indescribable mental changes as a help in understanding the mental life of patients with schizophrenia, a point very important for psychiatrists".

In Guttmann's experiments, and those with Maclay [9], it was striking to him that pure emotional reactions were observed in cases that were clinically diagnosed as endogenous depression. He speculated that future experimental work might lead to a better understanding of the complicated interplay of etiological factors in the origin of psychoses.

Stockings [11] described the results of a series of experiments performed with mescaline on himself and on a group of normal subjects, in an attempt to draw a comparison and correlation between the phenomena induced by mescaline and those seen in

naturally occurring psychoses. According to Stockings, the nature of the mental changes produced by mescaline were very similar to those observed in psychotic patients. The feeling of unreality, regarding both the self and the external world, often found in schizophrenia, was a typical feature of mescaline intoxication. Another striking parallel to schizophrenia and delusional cases were the morbid suspiciousness and often fully developed delusions and ideas of reference that always accompanied mescaline intoxications.

Based on his findings, Stockings emphasized the importance of mescaline in understanding the nature of mental disorders. He speculated that the causative agent in various mental illnesses was probably an endogenous toxic amine with chemical and pharmacological properties like those of mescaline.

LSD-25 Appears on the Scene

The next historical phase begins in 1943, when Albert Hofmann, a natural products chemist working at the Sandoz laboratories in Basel, Switzerland, accidently discovered the psychoactive effects of lysergic acid diethylamide (LSD-25), a compound he had first synthesized 5 years earlier [12]. Most of the psychedelic research from then on focused on LSD, likely due to its extreme potency and ready availability from Sandoz.

In 1947, the first scientific study on the effects of LSD was published by Werner Stoll, a psychiatrist affiliated with the University of Zurich [13]. In his clinical report, LSD was administered several times to 16 normal subjects and 6 treatment-resistant patients with schizophrenia. Doses given to normal subjects were generally 30 µg, but for the patients with schizophrenia varied from 20 to 130 µg. The treatment protocol was the same for both groups. The report included an extensive table with demographics for the normal subjects, along with their responses to LSD. In general, the effects started about 30 min after administration, reaching a peak about 1.5 h later, maintaining that level of effect for about 2 h, with the earliest return to normal at about 8 h. In normal subjects, LSD generally produced feelings of euphoria, visual patterns, feeling young, beautiful, and reborn. Subjects also reported being more sensitive to music. There was less of an effect in patients with schizophrenia, but none of them were made worse. Furthermore, first observations of rapid tolerance to LSD were made. The effects produced by LSD seemed to resemble those of mescaline, but investigators pointed out the uniquely high potency of LSD. They strongly encouraged further clinical research. Stoll did note that in low doses, *LSD seemed to facilitate the psychotherapeutic process* by allowing repressed material to pass easily into consciousness. ▶ **Table 1.**

Gion Condrau, working at the same hospital, treated 7 additional normal subjects and 30 treatment-resistant psychiatric patients, with similar results [14]. Again, psychiatric patients proved more resistant to the effects of LSD, even at doses of 100 µg. Condrau proposed that LSD might eventually find use for experimental induction of psychotic states. In a 1949 summary that included both clinical reports, Stoll reported [15] that LSD had by then been administered a total of 240 times; 40 administrations to 20 healthy volunteers and 200 administrations to 36 patients with psychiatric illness, mostly schizophrenia. In 40 administrations of LSD to the healthy volunteers, euphoria and visual effects were noted. Psychological effects of LSD in psychiatric patients were subtle and not pronounced. Ultimately, the therapeutic effect desired by Stoll and Condrau, based on the observation that LSD induced euphoria and a certain kind of mental shock through intoxication in healthy persons, did not occur in patients with schizophrenia.

Subsequently, Sandoz made LSD-25 available to research institutes and physicians, giving it the trade name Delysid, the name that Albert Hofmann had proposed. It is relevant to read the drug label that accompanied investigational samples of Sandoz LSD [16]:

Indications and dosage:

a) Analytical psychotherapy, to elicit release of repressed material and provide mental relaxation, particularly in anxiety states and obsessional neuroses. The initial dose is 25 µg (1/4 of an ampoule or 1 tablet). This dose is increased at each treatment by 25 µg until the optimum dose (usually between 50 and 200 µg) is found. The individual treatments are best given at intervals of 1 week.
b) Experimental studies on the nature of psychoses: By taking Delysid himself, the psychiatrist is able to gain an insight into the world of ideas and sensations of mental patients. Delysid can also be used to induce model psychoses of short duration in normal subjects, thus facilitating studies on the pathogenesis of mental disease. In normal subjects, doses of 25 to 75 µg are generally sufficient to produce a hallucinatory psychosis (on an average 1 µg/kg body weight). In certain forms of psychosis and in chronic alcoholism, higher doses are necessary (2 to 4 µg/kg body weight).

In 1950, Busch and Johnson [17] report a preliminary investigation of LSD in 21 psychotic patients. They described the mental effects as excitation, responding more readily to stimulation, and becoming talkative and emotional. The investigators reported LSD as having "profoundly influenced the course" of progress of 8 cases of psychoneurosis and emphasized the remembering and reliving of early traumatic experiences. Particularly impressive were the attempts of most patients to establish some kind of interpersonal relationship with the staff. Because 2 of the patients actually improved sufficiently to discontinue treatment, Busch and Johnson viewed these results as potentially being of value in psychotherapy. They then chose 8 additional patients undergoing psychotherapy for a trial with LSD. *This report appears to be the first literature mention of the use of LSD as an aid to psychotherapy*. According to the investigators, these 8 patients "had experiences which profoundly influenced the course of their progress". They concluded that LSD might offer a means for gaining access to chronically withdrawn patients and added that it also might serve as a new tool for shortening psychotherapy.

In 1951, Mayer-Gross [18] appears to have written the first English paper that compared the clinical action of mescaline and LSD. He noted that the subjective experience of an artificial psychosis of this kind is of great value to the psychiatrist, who, without danger, "can live in the strange worlds with which he has to deal in his daily work".

Stoll's previous observation of an LSD-induced euphoria led Savage [19] to carry out a study to determine whether that effect might be valuable in the treatment of depression. He reported studies on 5 normal controls and 15 depressed patients. The latter were started on a dose of 20 µg, which was increased daily up to

▶ **Table 1** Overview of representative studies with psychedelics in psychiatry and psychotherapy.

Year	Name [Ref]	Substance	Rationale	Design	Dosage	Outcome
1913	Knauer, Maloney [3]	Mescaline sulfate	Producing mental conditions similar to types of "insanity" to model and understand psychosis	Self-experiments and tests with other healthy subjects	Subcutaneous injections of an unknown dose	Detailed descriptions of qualitative aspects of the visual phenomena produced, noticed dramatic effects on time perception
1923	Fernberger [5]	Peyote	Examination of the psychological effects of peyote	Self-experiment	39 g of dried peyote buttons	Detailed description of the changes of sensory perception and consciousness
1932	Fernberger [8]	Peyote	Reproducing the situation in indigenous peyote ceremonies	Group setting with healthy persons	Infusion of boiled peyote buttons, 1 or 2 cups for each participant	Documentation of the physiological, psychological, and sensory effects as well as changes in consciousness
1936	Guttmann, Maclay [9]	Mescaline	Determining the value of mescaline as a therapeutic agent for derealization and depersonalization, investigating the character and pathogenesis of these syndromes	Clinical tests with 11 patients, each one getting a single low dose of a synthetic mescaline preparation, administered orally to avoid stronger symptoms of intoxication	0.1–0.2 g	Certain improvement of depersonalization symptoms; possible use of mescaline depersonalization as a model for therapeutic experiments; possible use of mescaline as an adjuvant for psychotherapy
1936	Guttmann [10]	Synthetic mescaline sulfate	Investigating the psychological effects of mescaline intoxication and determining its therapeutic value	Observations of 60 "mostly normal" subjects after administration of a single dose	100–400 mg, injected or orally administered	Usefulness of mescaline as psychotomimetic to understand the mental life of schizophrenics and as a therapeutic agent in states of depersonalization
1940	Stockings [11]	Mescaline	Investigating similarities, differences, and correlations between the phenomena induced by mescaline and those seen in naturally occurring psychoses	Self-experiment and experiments with healthy persons	0.2–0.5 g, administered orally	Mescaline as potential agent for a better understanding of mental disorders due to perceived similarities between the mental changes produced by mescaline and certain symptoms of psychotic patients
1947	Stoll [13]	LSD	Investigation of the psychological effects and therapeutic potentials of LSD	Clinical tests with 16 healthy persons and 6 schizophrenics	30 µg for healthy persons, varying doses from 20 to 130 µg for schizophrenics	Similarities to the range of effects of mescaline, assumption that LSD might facilitate the psychotherapeutic process in low doses
1949	Condrau [14]	LSD	Investigation of the psychological effects and therapeutic potentials of LSD	Clinical tests with 7 healthy persons and 30 treatment resistant psychiatric patients	Up to 100 µg	Confirmation of Stoll's results, proposition to use LSD for experimental induction of psychotic states
1950	Busch, Johnson [17]	LSD	Investigation of the effects of LSD on psychotic patients	Clinical tests with 21 psychotic patients; additional tests with 8 patients undergoing psychotherapy	30–40 µg	LSD could be an aid to shorten psychotherapy and may offer means for more readily gaining access to chronically withdrawn patients

▶ **Table 1** Continued.

Year	Name [Ref]	Substance	Rationale	Design	Dosage	Outcome
1952	Savage [19]	LSD	Determining the value of LSD-induced euphoria in the treatment of depression	Clinical tests with 5 healthy persons and 15 depressed patients	Increasing doses from 20 µg up to 100 µg	Thesis that LSD has no significant therapeutic advantage in depression but could be an adjuvant in some cases
1953	Katzenelbogen, Fang [20]	LSD, sodium amytal, methamphetamine	Comparing the usefulness of LSD, methamphetamine, and sodium amytal for narcosynthesis	Comparative study with 20 patients suffering from different psychotic, mostly schizophrenic, conditions	10–50 µg LSD, 5–20 mg methedrine, 0.3–0.5 g sodium amytal	"Ventilation of emotion" appeared to be more marked with LSD than with the other substances
1954	Anderson, Rawnsley [21]	LSD	Investigation of the effects of LSD on healthy persons and psychiatric patients	Clinical tests with 4 healthy persons and 19 psychiatric patients, Rorschach and Bender Gestalt test during intoxication	100–600 µg	Confirmation of earlier studies about the range of effects of LSD, noted the extremely variable action of LSD in the same subject on different occasions
1954	Sandison et al. [26–27]	LSD	Examination of the value of LSD for the treatment of psychoneuroses	Clinical tests with 36 patients suffering from psychoneurosis & allied conditions, completed by a 2-year follow-up	25–400 µg	Possibility to relive repressed memories with LSD, usefulness for the treatment of psychoneuroses
1957–1967	Leuner [40]	LSD	Psycholytic therapy in severe cases of chronic disorder and inability to work	Psychotherapeutic, specifically depth-psychological treatment combined with small doses of LSD in 82 severe cases of chronic disorder and inability to work, requiring 65.5 h of therapy with pre- & post-treatment per patient, over a period of 8 years	30–200 µg	53 patients (64 %) recovered or greatly improved
1959	Smith [24]	LSD, mescaline	Examination of the value of LSD and mescaline as adjuncts in the treatment of alcoholism	Clinical tests with 24 alcoholics, supplemented with superficial psychotherapy, occupational, and recreational therapy	A single dose of 200–400 µg LSD or 500 mg mescaline after 4 weeks of psychotherapy	Both substances are a useful adjunct to psychotherapy
1959	Chwelos et al. [31]	LSD	Follow-up study on earlier studies by Smith	Clinical tests similar to those of Smith, with 16 additional alcoholics	A single dose of 200–400 µg LSD or 500 mg mescaline after 4 weeks of psychotherapy	Most patients status improved
1959	Cohen, Eisner [33–34]	LSD	Proving the therapeutic value of LSD in different psychotic disorders	Clinical tests and follow up study with 29 patients with different diagnoses (depression, borderline schizophrenia, etc.) with a follow-up period from 6–17 months	Increasing doses from 25–125 µg	Slightly more than 70 % of the patients improved
1961	Maclean et al. [42]	LSD	Investigation of the value of LSD as an adjunct in psychotherapy of alcoholism	Clinical tests with 61 alcoholics and 18 months follow-up	400–1500 µg of LSD along with psychotherapy	46 patients with much or some degree of improvement
1961-1988	Bastiaans [48–49]	LSD, pentothal, psilocybin	Clinical trials to determine the value of LSD and pentothal in psychotherapy of war-related trauma	Unknown	Unknown	Unknown

▶ **Table 1** Continued.

Year	Name [Ref]	Substance	Rationale	Design	Dosage	Outcome
1963	Jensen, Ramsay [43–44]	LSD	Controlled clinical trial with 58 alcoholics to determine the value of LSD in the treatment of alcoholism	Average 2-months hospitalization, treatment program including 3 weekly Alcoholics Anonymous meetings, 1 single dose of LSD at the end of the program, 6–8 months follow-up	1 × 200 µg	By chi-squared test, significantly more of the alcoholics treated with LSD were abstinent or improved at the time of follow-up than of those who received group therapy without LSD or of the controls
1964	O'Reilly, Funk [51]	LSD	Clinical trial to determine the value of LSD in the treatment of alcoholism	Administration of 1 single dose of LSD to 68 chronic alcoholics, follow-up for 38 weeks	1 × 200 µg LSD	26 (38 %) remained abstinent during follow-up, the remaining 42 patients were classed as non-abstainers, whether or not they improved
1964	Kast, Collins [61–62]	LSD, dilaudid, meperidine	Comparison of the analgesic effect of LSD, meperidine, and dilaudid in the treatment of terminal illness	Double-blind clinical trial with 50 cancer patients	Consecutive administrations of 2 mg dihydromorphinone, 100 mg meperidine, and 100 µg LSD, with at least 6 h between each application	The analgesic effects of LSD lasted the longest; patients displayed peculiar disregard for the gravity of their situations, talked freely about their impending death with an affect most beneficial to their own psychic states
1965	Ludwig, Levine [53]	LSD	Determine the value of LSD and hypnodelic therapy in the treatment of narcotic addicts	Comparative controlled study with hypnodelic therapy for 70 "postnarcotic drug addicts"	2 µg of LSD per kilogram of bodyweight in distilled water, orally administered	Hypnodelic treatment consistently produced greater improvement than any of the other treatment conditions (LSD and psychotherapy, LSD alone, psychotherapy alone, or hypnotherapy) at both 2 weeks and 3 months after treatment
1969	Hollister et al. [52]	LSD, dextroamphetamine	Determining the value of LSD and dextroamphetamine in treatment of alcoholics without psychotherapy	Comparative study with 72 alcoholics, administration after a short discussion about their drinking problem, completed with 2-month and 6-month follow-up interviews	Single large dose of LSD (600 µg) or dextroamphetamine (60 mg)	At 2-month follow-up: 20 patients lost, significant improvement of those treated with LSD compared to those with dextroamphetamine At 6-month follow-up: differences between the treatment groups vanished, but all except 2 patients showed some degree of improvement
1969	Ludwig et al. [55]	LSD	Investigation of the differential effectiveness among 3 experimental LSD treatment conditions for alcoholism	Large-scale comparative controlled follow-up study with 176 male alcoholic patients, comparing hypnodelic therapy, LSD with and without psychotherapy, and a "no therapy" condition	3 µg of LSD per kilogram of bodyweight	None of the LSD treatment procedures produced any greater therapeutic benefit than the "no therapy" condition

▶ **Table 1** Continued.

Year	Name [Ref]	Substance	Rationale	Design	Dosage	Outcome
1970	Tomsovic, Edwards [22]	LSD	Determine the value of LSD in schizophrenic states and the treatment of alcoholics	Controlled clinical trial with LSD treatment for schizophrenic and non-schizophrenic patients who underwent an alcoholic rehabilitation program combined with questionnaire-type assessments for self-evaluation after 3, 6, and 12 months	One single dose of 500 µg to produce a "single overwhelming experience"	LSD-treated non-schizophrenic alcoholics had the highest percentage of abstainers from alcohol during each rating period, but differences were not statistically significant
1970	Pahnke et al. [54]	LSD	Determining the value of LSD in psychotherapy	One LSD session for 104 patients undergoing psychotherapy, completed by a 6-month follow-up	Administration of either 50 µg or 350–400 µg LSD	Supposed linkage between psychedelic-peak experiences and "rehabilitation," statistically significant reduction of alcohol consumption in the low and high dose groups
1970	Pahnke et al. [63]	LSD	Determining the value of psychedelic therapy in the treatment of cancer patients	Clinical trial with psychedelic therapy for 6 cancer patients	Varying doses from 200 to 300 µg	Decreased need for analgetics, improvement in mood and well-being
1973	Savage, McCabe [59]	LSD	Determining the value of LSD in the treatment of heroin addiction	Controlled residential study with a 12-months posttreatment period	300–450 µg	12-months continuous abstinence rates were 25 % with LSD and 5 % without LSD
1994	Strassmann et al. [69–70]	DMT	Generating dose-response data for the physiological effects of DMT on healthy persons, no therapeutic focus	Double-blind, saline placebo-controlled, randomized study with a group of 11 "experienced hallucinogen users"	0.05, 0.1, 0.2, and 0.4 µg per kg	DMT can be administered safely to experienced hallucinogen users, generated quantitative data as basis for further psychopharmacologic characterization of DMT's properties in humans
2006	Moreno et al. [77]	Psilocybin	Determining the value of psilocybin in the treatment of obsessive-compulsive-disorder (OCD)	Proof-of-concept double-blind safety study with 9 patients suffering from OCD, who received 4 escalating doses of psilocybin separated by at least 1 week	Subsequent administered doses of 100 µg/kg, 200 µg/kg and 300 µg/kg and a dose of 25 µg/kg randomly after the first dose	Marked decreases in OCD symptoms of variable degree in all subjects during 1 or more sessions, in some subjects symptom relief lasted for more than the 24-h assessment period
2006	Griffiths et al. [78]	Psilocybin	Determining the acute and persisting psychological effects of psilocybin on healthy persons	Double-blind study in 2 or 3 sessions with high doses of psilocybin relative to a comparison compound, with 30 volunteers	Oral administration of psilocybin (30 mg/70 kg) and methylphenidate hydrochloride (40 mg/70 kg) in counterbalanced order	Psilocybin produced a range of acute perceptual changes, subjective experiences, labile moods and increased measures of mystical experience; the experience had a substantial personal meaning and spiritual significance for the volunteers, leading to sustained positive changes in attitudes and behavior

▶ **Table 1** Continued.

Year	Name [Ref]	Substance	Rationale	Design	Dosage	Outcome
2011	Grob et al. [65]	Psilocybin	Determining the therapeutic value of psilocybin in advanced stages of cancer anxiety	Double-blind, placebo-controlled study of 12 patients with advanced-stage cancer and anxiety, completed by 6-month follow-up	0.2 mg/kg	State-Trait Anxiety Inventory trait anxiety subscale: significant reduction in anxiety at 1 and 3 months after treatment; Beck Depression Inventory: significant improvement of mood at 6 months
2014	Johnson et al. [81]	Psilocybin	Determining the usefulness of psilocybin in the treatment of nicotine addiction	3 administrations of psilocybin during a 15-week course of smoking cessation treatment, completed by a 6-month follow-up	1st administration 20 mg/70 kg, 2nd and 3rd administration 30 mg/70 kg	80 % of participants were abstinent at 6-month follow-up, abstinence rates were substantially higher than typical
2015	Bogenschutz et al. [80]	Psilocybin	Psilocybin-assisted treatment for alcohol dependence	Single-group proof-of-concept study of 10 volunteers with DSM-IV alcohol dependence during a 12-week, 14-session manualized inter-vention; oral administration of psilocybin in 1 or 2 sessions; follow-up for 9 months	1st session 0.3 mg/kg, 2nd session 0.4 mg/kg	Abstinence increased significantly following psilocybin administration, as well as decreases in craving
2016	Carhart-Harris et al. [82]	Psilocybin	Psilocybin administration as a therapy for treatment-resistant depression	Open-label feasibility trial of 12 patients with moderate-to-severe, unipolar, treatment-resistant major depression, receiving 2 oral doses	10 mg and 25 mg, 7 days apart	Depressive symptoms were markedly reduced 1 week after high-dose treatment, marked and sustained improvements in anxiety and anhedonia
2016	Griffiths et al. [67]	Psilocybin	Psilocybin-assisted psychotherapy in cancer patients	Randomized, double-blind, cross-over trial, investigating the effects of a very low and a very high dose of psilocybin administered in counterbalanced sequence with 5 weeks between sessions and a 6-month follow-up	Low dose of 1 or 3 mg/70 kg, high dose of 22 or 30 mg/70 kg	Substantial and sustained decreases in depression and anxiety
2016	Ross et al [79]	Psilocybin, Niacin	Psilocybin-assisted psychotherapy in cancer patients with depression and anxiety	Double-blind, placebo-controlled, crossover trial of 29 patients with cancer-related anxiety and depression, receiving a single-dose psilocybin or niacin, both in conjunction with psychotherapy, completed by 6.5-month follow-up	0.3 mg/kg	Rapid and sustained symptom reduction, 60–80 % of participants continued with clinically significant reductions in depression or anxiety, sustained benefits in existential distress and quality of life, as well as improved attitudes towards death

100 µg until a definite psychophysiological effect could be observed. All severely depressed patients of whatever diagnostic category admitted to the hospital were studied with follow-ups for about 6 months. Two suffering from involutional psychoses made complete recoveries to their prepsychotic state. Five schizoid persons with severe depressive reaction improved enormously and became free of depression. By contrast, in the control series of involutional psychoses, 2 patients recovered without specific therapy. Of 4 schizophrenic patients with depression, one signed out against advice, unimproved; the others were transferred to mental hospitals as unimproved. Within the limits of that sample, however, LSD did not appear to have a significant therapeutic advantage in depressed states, although it was suggested that it might be of value as an adjuvant in some cases.

Katzenelbogen and Fang [20] described administration of LSD to facilitate interviews with schizophrenic patients and compared its usefulness against methamphetamine and sodium amytal for narcosynthesis. After World War II, narcosynthesis was used to treat patients with "shell shock" (essentially renamed as posttraumatic stress disorder (PTSD) during the Viet Nam war era). This study was the first to consider the value of LSD in treating the emotional problems in many veterans returning from the battlefield. "Ventilation of emotion" appeared to be more marked with LSD than with methamphetamine or sodium amytal.

Anderson and Rawnsley [21] administered 10–600 µg of LSD on 58 occasions to 4 normal subjects and 19 psychiatric patients. In 6 cases, long-lasting favorable changes in the clinical picture were produced. The findings largely paralleled earlier investigations but drew attention to the extremely variable action of LSD in the same subject on different days. On some occasions the drug seemed to underscore the clinical picture, e. g., depression became enhanced, but the next day the same dose in the same patient might elicit a state of euphoria.

Treatment of Alcoholism and Addiction

Hoffer and Osmond first began using LSD to treat alcoholics in 1953 at the University Hospital at Saskatoon, Saskatchewan [22]. Initially they believed it might simulate delirium tremens, and the fear of that state might prompt alcoholics to stop drinking. That idea was soon abandoned, and emphasis was shifted toward the psychedelic aspects. From the beginning, it was not considered that LSD by itself could produce a major change in the alcoholic but was looked upon as an essential factor in an overall treatment program based on several therapeutic variables [23]. In the next 7 years, research with LSD in alcoholism was carried on almost exclusively in Canada and resulted in a series of reports, all of which concluded that it was either beneficial or at least very promising.

These early researchers collectively treated a fairly large population of patients but did not utilize adequate controls and were led by their subjective impression of what could be expected in treating alcoholics. They were enthusiastic because they had seen many patients profoundly moved by the experience and returning to society with new attitudes, hope, and enthusiasm. Subsequent findings in some of the controlled studies, however, seemed to indicate that those changes might be only transient and eventually faded when the alcoholic returned to society and old patterns regained power [22].

Smith [24] described treatment of 24 patients at University Hospital in Saskatoon using either LSD or mescaline as adjuncts to treatment with superficial psychotherapy supplemented by occupational and recreational therapy. Only the most difficult cases were taken into this study; all but 4 had tried alcoholics anonymous (AA) and were considered to have failed the program. It was thought that these drugs might make the patient "hit bottom" artificially and thereby render him more amenable to psychotherapy. Their trial was prompted by reports of numerous earlier investigators who had commented on the therapeutic value of these drugs [17, 25–30]. The group was an extremely unfavorable one prognostically, as one can see from the lack of response to previous treatment, and the frequency of complications. Patients entered 2–4 weeks of psychotherapy, followed by a single dose of 200–400 µg of LSD or 500 mg of mescaline. An extensive interview was conducted during the drug session. The material that emerged was discussed during the next few days, and the patient was discharged. A follow-up was carried out on all patients for periods ranging from 2 months to 3 years. Of the 24 patients originally studied, 12 were improved or much improved, with 12 unimproved. Considering "the refractory nature of the group," the investigators concluded that the results appear "sufficiently encouraging to merit more extensive and preferably controlled trials" and that the drugs were a useful adjunct to psychotherapy.

Chwelos et al. [31] followed up on the earlier studies by Smith [24, 32] and added 16 new patients who were also afflicted by alcohol use. The treatment was very similar, and 10 of these cases were much improved and 5 were improved.

Cohen and Eisner [33, 34] treated a total of 29 patients whose diagnoses varied from depressive states to borderline schizophrenia. They reported on 22 of these patients, who had a follow-up period varying from 6 to 17 months, and 16 of them were improved. But improvement with LSD therapy did not appear to be restricted to patients in any particular diagnostic category. The patient-therapist transaction seemed to be intensified in general, permitting more penetrating interpretations and a more direct approach to the basic problems. Patients usually described a perceptual component that consisted of "looking upon beauty and light". They felt greatly relaxed with internal insight, an awareness of their place in the environment, and a sense of order in life. The authors supposed that these feelings all "fused into a very meaningful episode," which could be significantly therapeutic.

In 1960, Cohen [35] sent a questionnaire to 62 investigators who had experience using either LSD or mescaline in normal subjects or patients, seeking information about adverse effects of both drugs. Forty-five respondents replied with data for almost 5,000 individuals who had received either LSD or mescaline on more than 25 000 occasions. There were no reported instances of prolonged physical side effects in the responses. Adverse reactions were nearly always due to psychological factors. Cohen concluded that, with proper precautions, these drugs were safe when given to healthy subjects. Occasional complications could be avoided by using several safeguards: 1) exclusion of prepsychotic individuals and those suffering from paranoid projections; 2) sufficient control of the patient during and after the experience; 3) constant attendance dur-

ing the session; 4) hospitalization for 24 h, especially if more than 1 µg/kg is given; 5) therapists should have experiences with the drug; 6) therapists must be prepared to handle a sudden upheaval of repressed and traumatic memories; 7) specially trained personnel; 8) a drug to counteract the effects of LSD; and 9) consultations after the session.

In 1959, the Josiah Macy Jr. Foundation (at times a Central Intelligence Agency conduit [36]) sponsored a conference on LSD-25, including prominent clinicians who discussed their psychotherapeutic experiences with the drug. This meeting revealed quite plainly the difficulties in determining the value of LSD as an adjuvant to psychotherapy. Nevertheless, Charles Savage described the conference as "most valuable," because it showed all at once results "ranging from the nihilistic conclusions of some to the evangelical ones of others" ([37] p. 193).

At that time, there were 2 different approaches to psychotherapy with LSD: "psycholytic" and "psychedelic" [38–40]. The psychedelic approach had its origin in North America, whereas psycholytic therapy was more commonly employed in Europe. The British psychiatrist Ronald Sandison was a pioneer of this approach, which he named in 1960.

Psycholytic therapy involved administering 50–200 µg of LSD to patients once or twice a week just prior to psychotherapy. The dosage was individually adjusted so that the patient remained oriented and in communication with the therapist, and able to realize the therapeutic character of the situation. Patients lay on a couch in a darkened room with 1 attendant and were occasionally visited by the physician. The drug-induced experience played only a supporting role in a primarily conventional psychoanalytical treatment because low dose LSD was believed to facilitate the recall of unconscious material. Typically, treatment continued for months to years, with between 10 and 50 psycholytic sessions being conducted [39]. In between the drug sessions were drug-free sessions, usually weekly or 2 times per week. Between 1953–1968, more than 7,000 patients were treated with this method [39].

In 1954, Sandison et al. [26] had examined the value of LSD for the treatment of psychoneuroses. They emphasized "the property possessed by the drug of disturbing the unconscious so that repressed memories are relived with remarkable clarity and a change to an infantile body image". In a 2-year follow-up of 30 of their original 36 patients, as well as results for treatment of 64 additional patients [27], they reported that, in total, 21 were recovered, 20 were greatly improved, 20 were moderately improved, and 32 were not.

Another European pioneer in psycholytic therapy was Hanscarl Leuner. His 1967 review was based on 10 years' clinical experience with psychotherapy aided by LSD and related substances such as psilocybin and CZ-74 [40]. During that period, more than 120 cases were carefully treated from a general psychotherapeutic and specifically depth-psychological point of view in the Psychiatric Clinic of the University of Göttingen, Germany. Leuner strictly employed Sandison's "Psycholytic Therapy," which was the only form of therapy using psychedelics practiced at 17 European centers. An example of his work was a follow-up study of 82 cases of completed psycholytic treatment, administered over a period of 8 years. The patients were taken from among the severest examples of chronic disorders. Sixty-four percent of them were reported as recovered or greatly improved. He summarized the nature of the treatment as requiring 65 h of therapy and suggested that the optimal length of treatment averaged 38 sessions with LSD. In his belief, psycholytic therapy was an essential branch of psychotherapy and, for methodological and clinical reasons, must be viewed as strictly separate from psychedelic therapy, which is based essentially on psychodynamics and advanced psychoanalysis. Leuner believed in the usefulness of psycholytic therapy and preferred it to other psychotherapeutic methods.

Psychedelic therapy was originally developed primarily for the treatment of addicts and people with personality disorders [41]. This procedure made induction of mystic or religious experiences the basis of its therapeutic action. It used a quasi-religious preparation of the patient, higher doses, specific surroundings, and music to favor evocation of deep-reaching insights and experiences. With this approach, patients underwent daily psychotherapy for weeks prior to a single high dose administration of LSD, typically 400 µg or more, to insure an overwhelming transcendental experience. Each session typically lasted from 12 to 16 h.

MacLean et al. [42] reported psychotherapy results from treatment of 61 alcoholics with LSD along with psychotherapy. They were drawn from patients admitted to the Hollywood Hospital (Westminster, British Columbia) for alcohol intoxication. Those subjects were considered to be difficult cases because many had experienced delirium tremens or had been unsuccessful in AA programs. After 3–18 months, half of them were much improved, whereas a quarter showed some degree of improvement.

Sven Jensen, a psychiatrist working in Weyburn, Saskatchewan, published the first controlled clinical trial of LSD in alcoholism in 1962 [43]. He developed a program based largely on the principles of AA. The treatment included weekly AA meetings. During 2 h of group psychotherapy, those who were not already familiar with the AA program were indoctrinated mainly by the other patients discussion. Toward the end of hospitalization, the patients were given LSD. The dosage (routinely 200 µg) usually produced an intense reaction in a nonalcoholic person; however, alcoholics were relatively resistant. Patients preparing for the LSD experience were told that it would not prevent them from drinking but would rather make them understand why they drink and what they could do about it. Of 58 patients who experienced the full program, and were followed up for 6–18 months, 34 had remained totally abstinent since discharge or stayed abstinent following a short experimental bout immediately after discharge; 7 were definitely drinking less than before; 13 were unimproved; and 4 were lost to follow-up. Of 35 patients who received group therapy without LSD, 4 were abstinent, 4 were improved, 9 were unimproved, and 18 were lost to follow-up. Of 45 controls, consisting of patients admitted to the hospital during the same period who received individual treatment by other psychiatrists, 7 were abstinent, 3 improved, 12 unimproved, and 23 lost to follow-up. By a chi-squared test, significantly more of the alcoholics treated with LSD were abstinent or improved at the time of follow-up than of those who received group therapy alone or of the controls.

Jensen and Ramsay [44] published a recap of the therapy as carried out by Jensen [43]. They provided several case studies to illustrate the nature of the therapy and certain individual's responses to it. The results of the Weyburn therapy program for alcoholism were considered "quite encouraging".

Unger [45] reviewed drug-induced rapid personality or behavior change following treatment with mescaline, LSD, or psilocybin. Different alcoholic treatment facilities reported not only complete abstinence for many of their patients after a single LSD session but also that a range of neurotic ailments were "practically evaporating". Unger concluded that the public health implications of drug-induced rapid personality change are apparently great and proposed further research. He cites a supporting reference to Wallace [46], who had stated:

"...the physiologic events of the general adaptation syndrome [in situations of massive emotion] establish a physicochemical milieu in which certain brains can perform a function of which they are normally incapable: a wholesale resynthesis that transforms intellectual insight into appropriate motivation, reduces conflict by partial or total abandonment of certain values and acceptance of others, and displaces old values to new, more suitable objects".

The largest and longest-running LSD project in the United States was the Spring Grove psychedelic research program, founded by Al Kurland and Sanford Unger in 1963 [47]. The project was continuously expanded until it was shut down in 1976, encompassing mainly the clinical research areas of alcoholism, neuroses, anxiety, and depression associated with terminal cancer or narcotic addiction.

Jan Bastiaans, a Dutch neurologist and professor of psychiatry at the State University of Leiden, became a major figure in the psychotherapeutic use of hallucinogens in the 1960s. He began using LSD or pentothal for psychotherapy of war-related trauma in 1961. The "Bastiaans method" was intended to allow patients to relive their (war) past. He claimed to be able to cure the worst cases. Unfortunately, many of his files were incomplete, so the effectiveness of his method could not be sufficiently validated [48, 49]. In the medical literature, his work and results have been mostly ignored.

Smith [50] discussed the 2 major criticisms of psychedelic therapy as they existed in 1964: that it was dangerous and ineffective. He was convinced that, when properly used, LSD appeared safe and cited, inter alia, a review by Hoffer [41] who states that extremely rare complications in most cases arise out of improper use of the drug. Indeed, Hoffer notes that only 5 out of 5,000 subjects described in the literature committed suicide, 4 doing so many months after an LSD session. "Considering that LSD has usually been given to the most hopeless psychiatric cases". Hoffer observed that "this is a remarkably low suicide rate" and speculated it might be likely "that LSD decreased the rate". Nevertheless, despite its low incidence, patients must still be monitored to prevent this serious event.

The more fundamental question considered by Smith [50] was whether LSD was effective in the treatment of alcoholism. But the main problem was that the whole field of evaluation of the effectiveness of treatment in alcoholism was unsatisfactory. Therefore, Smith noted that future studies should involve "methodologists" working in association with clinicians.

O'Reilly and Funk [51] reported on a study of 68 chronic alcoholics given treatment with single doses of 200 µg. Twenty-six of them attained sobriety during an average period of 38 weeks. The remaining 42 patients were classed as non-abstainers, whether or not they showed any improvement.

Hollister et al. [52] carried out a study that aimed to test the hypothesis that LSD given to alcoholics would produce a favorable response by itself, with little or no specific psychotherapy. They enrolled 72 alcoholic patients and compared the effects of a single large dose (600 µg) of LSD with a large (60 mg) dose of dextroamphetamine and included blind controls. The only "psychotherapeutic" intervention prior to administration of the drugs was a discussion with the patient of his drinking. Results were based on comparisons between the 2 treatments at 2-month and 6-month follow-up interviews. At the 2-month follow-up, the patients treated with LSD were doing significantly better than those treated with dextroamphetamine. By the time of the 6-month follow-up, however, differences between the treatments that were present at 2 months had vanished. Nevertheless, although many patients remained problem drinkers, the degree of their impairment had markedly improved. Only 2 of the 45 patients followed for 6 months were worse; all the others showed some degree of improvement.

Tomsovic and Edwards [22] recruited volunteers for LSD treatment from patients of an alcoholic rehabilitation program, including schizophrenic and nonschizophrenic patients. A second group of controls consisted of patients who had passed through the program and were part of an ongoing follow-up evaluation. This large group provided a stable measure of what was being achieved by the regular Program. A variety of questionnaire-type assessments were obtained, but the most important one was the patient's self-rating on a Drinking Adjustment Scale, made by checking categories ranging from complete abstinence to drinking heavily enough to require medical care. The patients received this questionnaire 3, 6, and 12 months after discharge from the hospital. When LSD benefits occurred, they tended to effect complete abstinence rather than a reduced consumption of alcohol. The greatest gain was seen in the nonschizophrenic LSD-treated patients, who had the highest percentages of abstaining. Even so, among the LSD-treated nonschizophrenic alcoholics, where a higher percentage abstained from alcohol, the differences were not statistically significant, and the authors could not conclude that LSD was beneficial.

The only controlled study of the treatment of narcotic addicts with LSD was that of Ludwig and Levine [53] who observed that addicts treated with "hypnodelic therapy" (simultaneous use of LSD, hypnosis, and psychotherapy) showed greater improvement at 2 months follow-up than addicts given other specific forms of treatment. Seventy patients with good suggestibility for hypnosis were selected, all of them "postnarcotic drug addicts". From the results, only the hypnodelic treatment condition consistently produced greater improvement than any of the other treatment conditions.

Pahnke et al. [54] reported the 6-month follow-up of 104 alcoholic patients who received 1 LSD session, each one given a dose of either 50 µg or 350–400 µg. Before that, patients were assessed based on a "global adjustment" scale, which included occupational, interpersonal, and residential factors as well as the patient's reaction to alcohol. Those with the most profound psychedelic-peak experiences comprised the highest percentage showing evidence of "rehabilitation". Both high and low dose groups showed a statistically significant reduction of alcohol consumption, leading investigators to the conclusion that while "not all patients were helped dramatically, none, even the most ill, appeared to have been harmed".

In order to follow up on their 1965 study, Ludwig et al. [55] carried out a large-scale controlled follow-up study with 176 male alcoholic patients. The 3-year investigation was designed to determine whether there would be differential effectiveness among 3 experimental LSD treatment conditions and a control treatment condition. For this purpose, hypnodelic therapy was compared with 2 other LSD techniques as well as with a "no therapy" condition. None of the treatment procedures produced any greater therapeutic benefit than the "no therapy" condition. By employing a controlled comparison design, they were able to ascertain that the patient's therapeutic responses following LSD procedures did not ensure any better treatment outcome than simple exposure to the hospital ward milieu [56].

Their treatment approach was flawed, however, as they did not employ the methodology of the many different studies that had reported at least some success. It seems apparent they believed that LSD as a chemical agent alone would be therapeutic and somehow lead to sobriety, while discounting the appropriate set and setting, as well as an assisting therapy, that were already known to be important for effectiveness.

Apparently, the treatments were carried out in a clinical facility with no provision for internalizing the experience, and they only spent 2 h of preparation that was mostly directed to gaining a family history. The study was based on 4 treatment groups: hypnosis and LSD ("hypnodelic therapy"), LSD and psychotherapy ("psychedelic therapy"), LSD with no psychotherapy, and a no therapy condition. The "psychotherapy," however, involved administering LSD, then simply encouraging the subjects to "think about their problems". In the LSD alone group, therapists did not engage in any dialogue with the patients. All sessions involving LSD lasted only 3 h.

Despite their attempt to design a setup that would allow them to compare the different therapeutic approaches, they obviously failed to appreciate the uniqueness of LSD and ignored the many studies that had reported some successes. Today, it is known that in treating nicotine addiction, the most favorable outcomes occurred when the participant has an overwhelming mystico-religious experience [57]. Yet, such experiences were very rare in the Levine et al. study, occurring only 8.4 % of the time ([56], p 105). Furthermore, Hoffer had stated in 1959, that those alcoholics "who have not had the transcendental experience are not changed; they continue to drink. However, the large proportion of those who have had it are changed" ([37], p. 114). As a conclusion, Levine et al. [56] stated that their negative findings produced such "inescapable conclusions about the purported efficacy of LSD for the treatment of alcoholism as to preclude any further investigation". ([56], p 9).

Unfortunately, at about this time, Jerome Levine took over as the chief of the Psychopharmacology Research Branch at NIMH. The negative conclusion of this large study, which he believed to be definitive, meant that Levine's attitudes toward LSD therapy, research, and funding would reflect the attitude at NIMH [47]. Thus, no further studies of the value of psychedelic-assisted psychotherapy for alcohol use disorder were reported.

A double-blind, controlled study of the effectiveness of psychedelic psychotherapy with alcoholics was conducted at the Spring Grove State Hospital in 1971 [58]. It was observed that at the 6-month follow-up, 53 % of the high dose group were rated by an independent evaluation team as "greatly improved" as opposed to 33 % of the low-dose group ($p < 0.05$). The outcome was supportive of the hypothesis that the LSD-induced psychedelic experience (which is more probable to occur with high dosages) can make a significant short-term contribution to the effectiveness of psychotherapy. Similar findings were reported in a study of heroin-addicted individuals by Savage and McCabe [59], showing significantly lower confirmed heroin use in a LSD group compared to the control group up to 12 months posttreatment.

Today, however, we know the results of a meta-analysis performed by Krebs and Johansen [60] of randomized controlled trials to evaluate the clinical efficacy of LSD in the treatment of alcoholism. They identified 6 eligible trials that included 536 participants and found evidence for a beneficial effect of LSD on alcohol misuse (OR, 1.96; 95 % CI, 1.36–2.84; $p = 0.0003$). Their conclusion was that a single dose of LSD, in the context of various alcoholism treatment programs, is associated with a decrease in alcohol misuse.

Psychedelics in Terminal Illness

Although a large proportion of early studies focused on the potential of psychedelic-assisted therapy to treat alcohol use disorder and other addictions, several of the most recent therapeutic studies of psychedelics have focused on treatment of patients with a life-threatening diagnosis, discussed in more detail later. This interest was sparked by studies in 1964 by Kast and Collins [61], who found that the analgesic effects of LSD in end-of-life patients lasted longer than those of meperidine or dilaudid (hydromorphone). They also observed that patients treated with LSD "displayed a peculiar disregard for the gravity of their situations, talked freely about their impending death with an affect considered inappropriate in our western civilization, but most beneficial to their own psychic states. This approach to their disease was noted usually for longer periods than the analgesic action lasted".

In a second paper, Kast [62] reported that LSD was capable of improving pre-terminal patients by making them more responsive to their environment and family. The LSD-induced imagery not only gave them aesthetic satisfaction but created a new will to live and a zest for experience that produced an exciting and promising outlook. In Kast's opinion, the short but profound impact on the dying patient was impressive.

There were more extensive investigations into the use of (primarily) LSD for the treatment of dying patients at the Spring Grove State Hospital in Baltimore, MD, that continued at the Maryland Psychiatric Research Center [54, 63]. As an example, in a group of 31 cancer patients treated with LSD-assisted psychotherapy, the pre- to post-treatment comparison of the indexes used as indicators of the degree of emotional and physical distress indicated that approximately 29 % of the patients showed dramatic improvement and another 41.9 % moderate improvement. Another 22.6 % remained essentially unchanged and only 6.4 % showed a decrement in the post-therapy ratings [64].

In restarting clinical research with psychedelics, especially psilocybin, it was the treatment of end-of-life patients that initially led to the most conclusive findings [65–67]. The Heffter Research Institute, which funded these more recent studies from philanthropic gifts, decided to focus on this patient group as potentially pro-

viding the strongest support for continuing to study the therapeutic use of psychedelics.

The End of LSD in Psychotherapy

Sandoz Pharmaceuticals ended its distribution of LSD in 1966 as a result of "unforeseen public reaction" [68]. Sandoz, and its inventor of LSD Albert Hofmann, never anticipated that a drug developed for understanding or mimicking mental illness would be widely used for recreational purposes. Its use by anti-war protesters and so-called hippies added to turbulent social unrest during the 1960s and indirectly led to the "drug war" started by the Nixon administration in the U.S. Compounding this problem, the FDA began evaluating applications to conduct research according to new, rigid criteria outlined in the Drug Amendments of 1962, which mandated that a drug be shown to be safe and effective prior to approval. But in contrast to most drugs, proving effectiveness for LSD and psychedelics was not easily defined, let alone measured.

The initial apparent successes of LSD psychotherapy in the 1950s had reflected the loose regulation of pharmaceutical research and development in that decade, which allowed psychiatrists to explore methods of treatment freely that blended biological and psychological techniques. LSD was used in numerous ways and for diverse purposes, yet all approaches were usually categorized under the mantle of therapy. The passage of the drug amendments of 1962 significantly changed that context [47]. Ongoing studies did continue, but no new studies were approved by the FDA.

Reinitiating Research with Psychedelics in the 1990s

After the Spring Grove State Hospital studies ended in 1976, there was no more clinical research with psychedelics until the study of intravenous DMT by Strassman in 1994 [69, 70], which did not focus on therapy.

Nevertheless, various in vitro and animal model studies were being reported showing that the crucial target of psychedelics was the brain serotonin 5-HT_{2A} receptor (see review [71]). Willins et al. [72] studied the regional and subcellular distribution of 5-HT_{2A} receptor-like immunoreactivity in rat cortex and reported dense labeling of apical dendrites of pyramidal cells. Confirmation of the role of 5-HT_{2A} receptors as the target for psychedelics in man came with the report by Vollenweider et al. [73] that the relatively 5-HT_{2A}-selective antagonist ketanserin blocked the psychoactive effects of psilocybin.

In the late 1990s brain imaging technologies began to be applied to the study of psychedelics. PET studies using the PET ligand [^{18}F]FDG correlated various changes in mood and perception after psilocybin administration in man with increases in cerebral metabolic rate of glucose (CMRglu) [74]. In a study by Hermle et al. [75], single-photon emission computed tomography (SPECT) was used to measure regional blood flow in male subjects given mescaline. The drug produced a pronounced increase in right anterior cortical regions; a "hyperfrontal" pattern with some emphasis on the right hemisphere, which was correlated with mescaline-induced effects.

In another human PET study using psilocybin and [^{18}F]FDG, Gouzoulis-Mayfrank et al. [76] measured metabolic rate of glucose (MRGlu) in several brain regions of interest when subjects performed an activation task. The metabolic pattern observed was characterized by relative hypermetabolism in the prefrontal and inferior temporal regions.

The first research to study potential therapeutic value for a psychedelic was carried out by Moreno and colleagues in 2006 [77]. In a small proof-of-concept safety study, psilocybin was given to 9 patients suffering from obsessive-compulsive disorder (OCD). Patients were given up to 4 escalating doses separated by at least 1 week. Marked decreases in OCD symptoms were observed in all subjects during 1 or more sessions. In some subjects, symptom relief lasted for more than the 24-h assessment period. Unfortunately, due to the small number of subjects as well as the absence of a dose-response relationship, this study was not conclusive.

More definitive research concerning the therapeutic value of psilocybin was carried out by Charles Grob [65]. A modest dose of psilocybin was administered to 12 adults with cancer and anxiety. The State-Trait Anxiety Inventory trait anxiety subscale demonstrated a significant reduction in anxiety at 3 months after treatment. The Beck Depression Inventory revealed an improvement of mood that reached significance at 6 months; the Profile of Mood States identified mood improvement that approached but did not reach significance.

Clinical studies began to proliferate in a new wave of research in the last 15 years. An abbreviated list of that research includes a study of psilocybin administration to normal subjects at Johns Hopkins University (JHU) [78], studies of psilocybin-assisted psychotherapy in cancer patients at JHU [67] and at New York University [79], psilocybin-assisted therapy for the treatment of alcohol use disorder at the University of New Mexico [80], for treating nicotine dependence at JHU [81], and a study of psilocybin as a therapy for treatment-resistant depression at Imperial College London [82]. They all reported statistically significant therapeutic improvement in the participants. Follow-up studies for this research have been carried out, as well as a number of studies using modern imaging technologies to understand better the effects of psychedelics on brain function. The growing number of such trials shows that we are entering a new phase of research with psychedelics.

Relative Safety of Psychedelics

In contrast to many other types of psychiatric drugs, psychedelics are relatively safe physiologically and are not considered drugs of dependence. A review by Strassman [83] has illustrated that point. Indeed, Nutt et al. [84] convened a panel of drug-harm experts to establish scores for 20 representative drugs that are relevant to the UK and which span the range of potential harms and extent of use. Using a multicriteria decision analysis (MCDA) approach, the panel members undertook a review of drug harms and identified 16 harm criteria. Nine relate to the harms that a drug produces in the individual and 7 to the harms to others both in the UK and overseas. Whereas alcohol and heroin had overall harm scores (out of 100) of 72 and 55, respectively, LSD and psilocybin-containing mushrooms had 2 of the 3 lowest harm scores, of 7 and 6, respectively. Interestingly, a survey of 190,000 adult respondents pooled from

the last 5 available years of the National Survey on Drug Use and Health (2008–2012) found that lifetime classic psychedelic use was associated with a significantly reduced odds of past month psychological distress, past year suicidal thinking, past year suicidal planning, and past year suicide attempt [85].

As a result of the positive outcomes of many of the recent clinical studies, there is a popular cry today to decriminalize or even legalize psychedelics like psilocybin and ayahuasca. Despite their low degree of relative harm, however, use of psychedelics does involve unique *psychological* risks. The most likely risk is overwhelming distress during the drug effect (a "bad trip"), which could lead to potentially dangerous behavior such as leaving the study site. Less common are prolonged psychoses triggered by these substances. A list of safeguards against these risks has been published [86] and includes dose control, patient screening, preparation follow-up, and session supervision in a medical facility [87].

Psychiatry is now recognizing the promise that psychedelics seemed to offer more than half a century ago. As a result psychiatry may be undergoing a paradigm shift with respect to treatment of depression, anxiety, addictions, and other illnesses [88].

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Conflicts of Interest

The authors declare that they have no conflict of interest.

References

[1] Dyck E. Flashback: psychiatric experimentation with LSD in historical perspective. Can J Psychiatry 2005; 50: 381–388

[2] Hoff P. The Kraepelinian tradition. Dialogues Clin Neurosci 2015; 17: 31–41

[3] Knauer A, Maloney WJMA. A preliminary note on the psychic action of mescalin, with special reference to the mechanism of visual hallucinations. J Nerv Ment Dis 1913; 40: 425–436

[4] Beringer K. Experimentelle psychosen durch mescalin. Vortrag, gehalten auf der südwestdeutschen psychiaterversammlung in Erlangen 1922. Zeitschrift für die gesamte Neurologie und Psychiatrie 1923; 84: 426–433

[5] Fernberger SW. Observations on taking peyote "(Anhalonium Lewinii)". Am J Psych 1923; 34: 267–270

[6] Rouhier A. Le Peyotl (Echinocactus Wttliamsii Lem.) La plante qui fait les yeux emerveilles. Paris: Doin;; 1927

[7] Brown AF. Reviews the book, Le Peyotl (Echinocactus Williamsii Lem.): La plante qui fait les yeux emerveilles by Alexander Rouhier (1927). Psychol Bull 1927; 24: 656–658

[8] Fernberger SW. Further observations on peyote intoxication. J Abnorm Soc Psychol 1932; 26: 367–378

[9] Guttmann E, Maclay WS. Mescalin and depersonalization: therapeutic experiments. J Neurol Psychopathol 1936; 16: 193–212

[10] Guttmann E. Artificial Psychoses produced by mescaline. J Ment Sci 1936; 82: 203–221

[11] Stockings GT. A clinical study of the mescaline psychosis, with special reference to the mechanism of the genesis of schizophenic and other psychotic states. J Mental Sci 1940; 86: 29–47

[12] Nichols DE. Dark classics in chemical neuroscience: Lysergic acid diethylamide (LSD). ACS Chem Neurosci 2018; 9: 2331–2343

[13] Stoll WA. 11. Lysergsäure-diäthylamid, ein Phantastikum aus der Mutterkorngruppe. Schweiz Arch Neurol Psychiatr 1947; 60: 279–323

[14] Condrau C. Klinische ergahrungen an geisteskranken mit lysergsäure-diäthylamide. Acta Psychiat Scand 1949; 24: 9–32

[15] Stoll A. Ein neues, in sehr kleinen Mengen wirksames Phantastikum. Schweiz Arch Neurol Psychiatr 1949; 64: 483–484

[16] Hofmann A. LSD, My Problem Child: Reflections on Sacred Drugs, Mysticism, and Science. Los Angeles, CA: J.P. Tarcher; 1983

[17] Busch AK, Johnson WCLSD. 25 as an aid in psychotherapy; preliminary report of a new drug. Dis Nerv Syst 1950; 11: 241–243

[18] Mayer-Gross W. Experimental psychoses and other mental abnormalities produced by drugs. Br Med J 1951; 2: 317–321

[19] Savage C. Lysergic acid diethylamide; a clinical-psychological study. Am J Psychiatry 1952; 108: 896–900

[20] Katzenelbogen S, Fang AD. Narcosynthesis effects of sodium amytal, methedrine and L.S.D-25. Dis Nerv Syst 1953; 14: 85–88

[21] Anderson EW, Rawnsley K. Clinical studies of lysergic acid diethylamide. Monatsschr Psychiatr Neurol 1954; 128: 38–55

[22] Tomsovic M, Edwards RV. Lysergide treatment of schizophrenic and nonschizophrenic alcoholics: a controlled evaluation. Q J Stud Alcohol 1970; 31: 932–949

[23] Hoffer A. A program for the treatment of alcoholism: LSD, malvaria and nicotinic acid.In: Abramson HA, editor. The Use of LSD in Psychotherapy and Alcoholism. Indianapolis: Bobbs-Merrill; 1967: 343–406

[24] Smith CM. A new adjunct to the treatment of alcoholism: the hallucinogenic drugs. Q J Stud Alcohol 1958; 19: 406–417

[25] Sandison RA. Psychological aspects of the LSD treatment of the neuroses. J Ment Sci 1954; 100: 508–515

[26] Sandison RA, Spencer AM, Whitelaw JD. The therapeutic value of lysergic acid diethylamide in mental illness. J Ment Sci 1954; 100: 491–507

[27] Sandison RA, Whitelaw JD. Further studies in the therapeutic value of lysergic acid diethylamide in mental illness. J Ment Sci 1957; 103: 332–343

[28] Denber HC, Merlis S. A note on some therapeutic implications of the mescaline-induced state. Psychiatr Q 1954; 28: 634–640

[29] Frederking W. Intoxicant drugs (mescaline and lysergic acid diethylamide) in psychotherapy. J Nerv Ment Dis 1955; 121: 262–266

[30] Abramson HA. Lysergic acid diethylamide (LSD-25). III. As an adjunct to psychotherapy. J Psychol 1955; 39: 127–155

[31] Chwelos N, Blewett DB, Smith CM et al. Use of d-lysergic acid diethylamide in the treatment of alcoholism. Q J Stud Alcohol 1959; 20: 577–590

[32] Smith CM. Some reflections on the possible therapeutic effects of the hallucinogens; with special reference to alcoholism. Q J Stud Alcohol 1959; 20: 292–301

[33] Eisner BG, Cohen S. Psychotherapy with lysergic acid diethylamide. J Nerv Ment Dis 1958; 127: 528–539

[34] Cohen S, Eisner BG. Use of lysergic acid diethylamide in a psychotherapeutic setting. AMA Arch Neurol Psychiatry 1959; 81: 615–619

[35] Cohen S. Lysergic acid diethylamide: side effects and complications. J Nerv Ment Dis 1960; 130: 30–40

[36] Lee MA, Shlain B. Acid Dreams: The Complete Social History of LSD: The CIA, The Sixties, and Beyond. New York: Grove Press; 1985

[37] Group Interchange. In: Abramson HA, editor. The Use of LSD in Psychotherapy. New York: Josiah Macy Jr Foundation Publications; 1960: 304

[38] Faillace LA. Clinical use of psychotomimetic drugs. Compr Psychiatry 1966; 7: 13–20

[39] Passie T. Psycholytic and psychedelic therapy research: A complete international bibliography 1931–1995. Hannover, Germany: Laurentius Publishers; 1997

[40] Leuner H. Present state of psycholytic therapy and its possibilities. In: Abramson HA, editor. The Use of of LSD in Psychotherapy and Alcoholism Indianapolis. Bobbs-Merrill; 1967: 101–116

[41] Hoffer A. D-lysergic acid diethylamide (LSD): a review of its present status. Clin Pharmacol Ther 1965; 6: 183–255

[42] Maclean JR, Macdonald DC, Byrne UP et al. The use of LSD-25 in the treatment of alcoholism and other psychiatric problems. Q J Stud Alcohol 1961; 22: 34–45

[43] Jensen SE. A treatment program for alcoholics in a mental hospital. Q J Stud Alcohol 1962; 23: 315–320

[44] Jensen SE, Ramsay R. Treatment of chronic alcoholism with lysergic acid diethylamide. Can Psychiat Assn J 1963; 8: 182–188

[45] Unger SM. Mescaline, LSD, psilocybin, and personality change. Psychiatry 1963; 26: 111–125

[46] Wallace AF. Stress and rapid personality changes. Int Rec Med Gen Pract Clin 1956; 169: 761–774

[47] Oram M. The Trials of Psychedelic Therapy: LSD Psychotherapy in America. Baltimore, MD: Johns Hopkins University Press; 2018

[48] Alper K, Beal D, Kaplan CD. A contemporary history of ibogaine in the United States and Europe. In: Alper KR, Glick SD, Editors. Ibogaine: Proceedings from the First Internation Conference. First ed. New York: Academic Press; 2001: 250–282

[49] Bastiaans J. Mental liberation facilitated by the use of hallucinogenic drugs.In: Grinspoon L, Bakalar, JB, Editor. Psychedelic Reflections. New York: Human Sciences Press, Inc; 1983: 143–152

[50] Smith CM. Exploratory and controlled studies of lysergide in the treatment of alcoholism. Q J Stud Alcohol 1964; 25: 742–747

[51] O'Reilly PO, Funk A. Lsd in chronic alcoholism. Can Psychiatr Assoc J 1964; 9: 258–261

[52] Hollister LE, Shelton J, Krieger G. A controlled comparison of lysergic acid diethylamide (LSD) and dextroamphetmine in alcoholics. Am J Psychiatry 1969; 125: 1352–1357

[53] Ludwig AM, Levine J. A controlled comparison of five brief treatment techniques employing lsd, hypnosis, and psychotherapy. Am J Psychother 1965; 19: 417–435

[54] Pahnke WN, Kurland AA, Unger S et al. The experimental use of psychedelic (LSD) psychotherapy. JAMA 1970; 212: 1856–1863

[55] Ludwig A, Levine J, Stark L et al. A clinical study of LSD treatment in alcoholism. Am J Psychiatry 1969; 126: 59–69

[56] Ludwig AM, Levine J, Stark LHLSD et al. Clinical Study of Treatment Efficacy. Springfield, IL: Charles C. Thomas; 1970

[57] Garcia-Romeu A, Griffiths RR, Johnson MW. Psilocybin-occasioned mystical experiences in the treatment of tobacco addiction. Curr Drug Abuse Rev 2014; 7: 157–164

[58] Pahnke WN, Kurland AA, Unger S et al. The experimental use of psychedelic (LSD) psychotherapy. Int Z Klin Pharmakol Ther Toxikol 1971; 4: 446–454

[59] Savage C, McCabe OL. Residential psychedelic (LSD) therapy for the narcotic addict. A controlled study. Arch Gen Psychiatry 1973; 28: 808–814

[60] Krebs TS, Johansen PO. Lysergic acid diethylamide (LSD) for alcoholism: meta-analysis of randomized controlled trials. J Psychopharmacol 2012; 26: 994–1002

[61] Kast EC, Collins VJ. Lysergic acid diethylamide as an analgesic agent. Anesthes Analg 1964; 43: 285–291

[62] Kast E. LSD and the dying patient. Chic Med Sch Q 1966; 26: 80–87

[63] Pahnke WN, Kurland AA, Unger S et al. Psychedelic therapy (utilizing LSD) with cancer patients. J Psychedelic Drugs 1970; 3: 63–75

[64] Grof S, Goodman LE, Richards WA et al. LSD-assisted psychotherapy in patients with terminal cancer. Int Pharmacopsychiatry 1973; 8: 129–144

[65] Grob CS, Danforth AL, Chopra GS et al. Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. Arch Gen Psychiatry 2011; 68: 71–78

[66] Ross S. Therapeutic use of classic psychedelics to treat cancer-related psychiatric distress. Int Rev Psychiatry 2018; 30: 317–330

[67] Griffiths RR, Johnson MW, Carducci MA et al. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: a randomized double-blind trial. J Psychopharmacol 2016; 30: 1181–1197

[68] Anon. Sole U.S. distributor surrenders its right to handle drug LSD. Globe and Mail. Toronto, Canada: The Woodbridge Company 1966: 1

[69] Strassman RJ, Qualls CR, Uhlenhuth EH et al. Dose-response study of N,N-dimethyltryptamine in humans. II. Subjective effects and preliminary results of a new rating scale. Arch Gen Psychiatry 1994; 51: 98–108

[70] Strassman RJ, Qualls CR. Dose-response study of N,N-dimethyltryptamine in humans. I. Neuroendocrine, autonomic, and cardiovascular effects. Arch Gen Psychiatry 1994; 51: 85–97

[71] Nichols DE. Hallucinogens. Pharmacol Ther 2004; 101: 131–181

[72] Willins DL, Deutch AY, Roth BL. Serotonin 5-HT2A receptors are expressed on pyramidal cells and interneurons in the rat cortex. Synapse 1997; 27: 79–82

[73] Vollenweider FX, Vollenweider-Scherpenhuyzen MF, Babler A et al. Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action. Neuroreport 1998; 9: 3897–3902

[74] Vollenweider FX, Leenders KL, Scharfetter C et al. Positron emission tomography and fluorodeoxyglucose studies of metabolic hyperfrontality and psychopathology in the psilocybin model of psychosis. Neuropsychopharmacology 1997; 16: 357–372

[75] Hermle L, Gouzoulis-Mayfrank E, Spitzer M. Blood flow and cerebral laterality in the mescaline model of psychosis. Pharmacopsychiatry 1998; 31: 85–91

[76] Gouzoulis-Mayfrank E, Schreckenberger M, Sabri O et al. Neurometabolic effects of psilocybin, 3,4-methylenedioxyethylamphetamine (MDE) and d-methamphetamine in healthy volunteers. A double-blind, placebo-controlled PET study with [18F]FDG. Neuropsychopharmacology 1999; 20: 565–581

[77] Moreno FA, Wiegand CB, Taitano EK et al. Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder. J Clin Psychiatry 2006; 67: 1735–1740

[78] Griffiths RR, Richards WA, McCann U et al. Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. Psychopharmacology (Berl) 2006; 187: 268–283

[79] Ross S, Bossis A, Guss J et al. Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. J Psychopharmacol 2016; 30: 1165–1180

[80] Bogenschutz MP, Forcehimes AA, Pommy JA et al. Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study. J Psychopharmacol 2015; 29: 289–299

[81] Johnson MW, Garcia-Romeu A, Cosimano MP et al. Pilot study of the 5-HT2AR agonist psilocybin in the treatment of tobacco addiction. J Psychopharmacol 2014; 28: 983–992

[82] Carhart-Harris RL, Bolstridge M, Rucker J et al. Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. Lancet Psychiatry 2016; 3: 619–627

[83] Strassman RJ. Adverse reactions to psychedelic drugs. A review of the literature. J Nerv Ment Dis 1984; 172: 577–595

[84] Nutt DJ, King LA, Phillips LD et al. Drug harms in the UK: a multicriteria decision analysis. Lancet 2010; 376: 1558–1565

[85] Hendricks PS, Thorne CB, Clark CB et al. Classic psychedelic use is associated with reduced psychological distress and suicidality in the United States adult population. J Psychopharmacol 2015; 29: 280–288

[86] Johnson M, Richards W, Griffiths R. Human hallucinogen research: guidelines for safety. J Psychopharmacol 2008; 22: 603–620

[87] Johnson MW, Hendricks PS, Barrett FS, et al. Classic psychedelics: an integrative review of epidemiology, mystical experience, brain network function, and therapeutics. Pharmacol Ther 2018

[88] Nichols DE, Johnson MW, Nichols CD. Psychedelics as medicines: an emerging new paradigm. Clin Pharmacol Ther 2017; 101: 209–219