Efficacy and Enlightenment: LSD Psychotherapy and the Drug Amendments of 1962

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Abstract. The decline in therapeutic research with lysergic acid diethylamide (LSD) in the United States over the course of the 1960s has commonly been attributed to the growing controversy surrounding its recreational use. However, research difficulties played an equal role in LSD psychotherapy's demise, as they frustrated researchers' efforts to clearly establish the efficacy of treatment. Once the Kefauver Harris Drug Amendments of 1962 introduced the requirement that proof of efficacy be established through controlled clinical trials before a drug could be approved to market, the value of clinical research became increasingly dependent on the scientific rigor of the trial's design. LSD psychotherapy's complex method of utilizing drug effects to catalyze a psychological treatment clashed with the controlled trial methodology on both theoretical and practical levels, making proof of efficacy difficult to obtain. Through a close examination of clinical trials performed after 1962, this article explores how the new emphasis on controlled clinical trials frustrated the progress of LSD psychotherapy research by focusing researchers' attention on trial design to the detriment of their therapeutic method. This analysis provides a new perspective on the death of LSD psychotherapy and explores the implications of the Drug Amendments of 1962. ***Keywords:*** LSD, controlled clinical trial, psychiatry, psychotherapy, psychopharmacology, Drug Amendments of 1962, efficacy, drug regulation.

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The fate of lysergic acid diethylamide (LSD) research in the 1960s has typically been linked to controversy. LSD entered the United States in 1949 and immediately became a drug of great interest to psychiatrists. Therapeutic research with LSD flourished, with psychiatrists using it to promote more effective psychotherapy, or exploring how the powerful mystical, or psychedelic, LSD experience could transform aspects of personality and behavior in patients, including leading to sobriety in alcoholics. However, in the 1960s, public controversy over LSD's increasing recreational use grew to fever pitch. Most accounts of LSD psychotherapy's history have argued that this uproar doomed legitimate research by tarnishing the drug's reputation, discouraging researchers from using it, and criminalizing the use of the drug, making it harder to gain approval for research.[1] Alternatively, Steven Novak has argued that prior to the LSD abuse scandal, concern over LSD's dangers, resulting from the irresponsible use of the drug by several researchers in Southern California, had already led to a government "crackdown" on LSD.[2]

The LSD controversies certainly did have a major impact on research. In 1966, they resulted in Sandoz Pharmaceuticals withdrawing its sponsorship of LSD investigations.[3] Consequently, LSD's development into a marketable pharmaceutical became much less likely, as researchers were not normally responsible for pushing drugs through the Food and Drug Administration's (FDA) New Drug Application process without the sponsorship of a pharmaceutical company. Historians have also pointed to the experiences of individual researchers who cited the controversy, and subsequent difficulties in obtaining grants and

1. See Erika Dyck, *Psychedelic Psychiatry: LSD from Clinic to Campus* (Baltimore: The Johns Hopkins University Press, 2008); Kimberly Allyn Hewitt, "Psychedelics and Psychosis: LSD and Changing Ideas of Mental Illness, 1943–1966" (PhD diss., University of Texas, 2002); Martin A. Lee and Bruce Shlain, *Acid Dreams: The Complete Social History of LSD: The CIA, the Sixties, and Beyond* (New York: Grove Press, 1985); Jay Stevens, *Storming Heaven: LSD and the American Dream* (London: Heinemann, 1987); Robert F. Ulrich and Bernard M. Patten, "The Rise, Decline, and Fall of LSD," *Perspect. Biol. Med.*, 1991, *34*, 561–78.

2. Steven J. Novak, "LSD before Leary: Sidney Cohen's Critique of 1950s Psychedelic Research," *Isis*, 1997, *88*, 87–110.

3. *Organization and Coordination of Federal Drug Research and Regulatory Programs: LSD*, Hearings before the Subcommittee on Executive Reorganization of the Committee on Government Operations, U.S. Senate, 89th Congress, 2nd Session, 24–26 May 1966 (Washington: U.S. Government Printing Office, 1966), 80–81.

supplies of LSD, to explain their withdrawal from the field.[4] However, these hurdles did not end LSD psychotherapy research, which survived the controversies of the 1960s, before finally coming to a close in the early 1970s. LSD's criminalization did not prohibit research and, until 1970, permission to conduct clinical research with LSD was obtained through the same process as any other drug.[5] Additionally, many drugs, such as morphine, maintained dual lives as illegal street drugs, and valuable and legitimate tools of medicine. Indeed, a similar public, medical, and political outcry over the dangers of medical and nonmedical abuse of amphetamines occurred concurrent with the LSD controversies of the mid to late 1960s. Amphetamine abuse was a target of the same prohibiting legislation as LSD, yet the drug retained a legitimate medical use.[6]

If controversy cannot completely explain the downfall of LSD psychotherapy, more attention needs to be paid to the later years of clinical research. Analyzing these trials reveals that the primary point of contention amongst researchers was LSD psychotherapy's efficacy. A central question in the history of LSD therefore becomes, why, after more than twenty years of research, had a consensus on LSD psychotherapy's efficacy not been reached? Answering this question requires contextualizing LSD research within the major changes in the regulation and practice of pharmaceutical research and development that occurred in the period, represented and regulated by the 1962 Kefauver Harris Amendments to the federal Food, Drug and Cosmetic Act (referred to hereafter as the Drug Amendments of 1962). Doing so not only provides a more nuanced perspective on the downfall of LSD psychotherapy research, but also explores the significance of those amendments.

4. Dyck, *Psychedelic Psychiatry*, 126.

5. In 1970, LSD was listed as a Schedule I drug under the *Controlled Substances Act of 1970*, 91 P.L. 513; 84 Stat. 1236, 27 October 1970. This law still did not ban the use of LSD in research, but required researchers to receive approval from the Bureau of Narcotics and Dangerous Drugs (later Drug Enforcement Administration). Richard Elliot Doblin, "Regulation of the Medical Use of Psychedelics and Marijuana" (PhD diss., Harvard University, 2000), 48–50.

6. LSD and amphetamine were both targets of the *Drug Abuse Control Amendments of 1965*, 89 P.L. 74; 79 STAT. 226, 19 July 1965, and the *Controlled Substances Act of 1970*, though they were scheduled differently in the latter, allowing amphetamine's continued medical use. For the medical and nonmedical history of amphetamine, see Nicolas Rasmussen, *On Speed: The Many Lives of Amphetamine* (New York: New York University Press, 2008).

The Drug Amendments of 1962 introduced the formal requirement for proof of efficacy through controlled clinical trials before a drug could be approved for sale.[7] As a result, the value of clinical trials increasingly became dependent on the scientific rigor of their design, and the gold standard became the randomized double-blind controlled trial. In its purest form, the method involved randomly assigning patients to receive either the experimental treatment or a placebo, with both researchers and patients "blind" to the assignment until after the conclusion of the trial. Emphasis was placed on the need for large patient populations and sophisticated statistical analysis to determine the significance of results. This technique theoretically allowed the objective assessment of drugs, as all extrapharmacological factors that could influence the outcome of a treatment were equally present in the experimental and control groups. Therefore, any statistically significant difference in the results between the groups could only be due to the drug.

However, this method was not well suited to test all treatments, particularly those that utilized psychological elements, and it carried with it the assumption that drug therapies worked through a direct biological action. Isolating psychological factors from drug effects widened the boundary between psychiatry's pharmaceutical and psychological treatments—drugs were treated as acting objectively on the brain, psychotherapy as acting subjectively on the mind. This development caused considerable difficulty for LSD psychotherapists, whose treatment was neither purely pharmaceutical nor psychological.

The Drug Amendments of 1962 frustrated the progress of LSD psychotherapy research by focusing researchers' attention on clinical trial design, to the detriment of their therapeutic method. This argument will be explored through an analysis of how the theory and method of randomized controlled trials clashed with LSD psychotherapy, and then a close analysis of four clinical trials performed after 1962 to display the effect of the Amendments on LSD psychotherapy research. These trials all tested a variant of psychedelic therapy, a form of LSD psychotherapy designed to treat alcoholism. This was most widely tested form of LSD psychotherapy in the United States, the subject of research from the late 1950s until the start of the 1970s.

7. *Drug Amendments of 1962*, 87 P.L. 781; 76 Stat. 780, 10 October 1962. Also known as the Kefauver Harris Amendments.

Canadian researchers Humphry Osmond, Abram Hoffer, and Alfred M. Hubbard had developed psychedelic therapy in the mid to late 1950s. Their novel treatment employed the power of the psychedelic experience to promote strong changes in attitude, perspective, and behavior in the patient. The treatment consisted of an intensive course of psychotherapy, leading to a single high-dose LSD session. The psychotherapy prepared the patient for the drug's effects—helping to ensure a psychedelic response—and educated the therapist in the patient's history and problems, helping them to best direct the treatment toward beneficial results. The LSD session took place in a comfortably furnished room, with visual and auditory stimuli, which helped relax the patient and bring them to the psychedelic reaction. The psychiatrist and a nurse stayed with the patient for the full ten to twelve hours of the drug's action, giving supportive guidance. Psychotherapy in the days after the LSD session helped to integrate the patient's experiences. By the start of the 1960s, this was a well-established method, which had shown great success for a number of researchers.[8]

Historians such as Kimberly Hewitt, Martin A. Lee, and Bruce Shlain have recognized that the FDA and critics increasingly demanded the results of controlled clinical trials to support claims of LSD's therapeutic efficacy, and that performing such trials with LSD was very difficult.[9] Erika Dyck has further explored how Osmond and Hoffer protested that controlled trials were not appropriate for evaluating LSD psychotherapy. Their refusal to adopt the methodology began the discrediting of their research, which the public controversy finished off.[10] However, the later 1960s American LSD research, which attempted to conform to the controlled trial requirements, as well as the greater implications of the methodological conflicts, not only for the fate of

8. Abram Hoffer, "A Program for the Treatment of Alcoholism: LSD, Malvaria and Nicotinic Acid," in *The Use of LSD in Psychotherapy and Alcoholism*, ed. Harold A. Abramson (Indianapolis: Bobbs-Merrill, 1967), 343–406, 343–75; J. Ross MacLean et al., "The Use of LSD-25 in the Treatment of Alcoholism and Other Psychiatric Problems," *Q. J. Stud. Alcohol*, 1961, *22*, 34–45. For a U.S. replica of the Canadian research, see Charles Savage, "LSD, Alcoholism and Transcendence," *J. Nerv. Ment. Dis.,* 1962, *135*, 429–35; and J. N. Sherwood, M. J. Stolaroff, and W. W. Harman, "The Psychedelic Experience—A New Concept in Psychotherapy," *J. Neuropsychiatry,* 1962, *4*, 69–80.

9. Hewitt, "Psychedelics and Psychosis," 214, 294; Lee and Shlain, *Acid Dreams,* 90.

10. Dyck, *Psychedelic Psychiatry,* 47–51, 73–78, 120.

LSD psychotherapy but for psychiatry and pharmaceutical regulation, has remained largely unexplored.

The rise of the controlled clinical trial, the growth in the power of the FDA, and the passage of the Drug Amendments of 1962 have been topics of inquiry for a number of scholars. Harry Marks, Daniel Carpenter, and Arthur Daemmrich have analyzed the role of pressure groups within the scientific community, political reformers, and medical tragedies in bringing about these significant changes.[11] More specifically in regard to psychiatry, David Healy and Edward Shorter have argued that the 1962 Amendments had ramifications more complex than simply ensuring the efficacy of drugs. Healy has explored how the Amendments supported a medical, or "bacteriological," model of mental illness, by requiring specific treatments for specific diseases, which has helped to shape the modern conception and treatment of depression.[12] Shorter argues that the way in which the Amendments were enforced has resulted in an industry that favors the newest, rather than most effective, drugs.[13] My analysis further develops this research by exploring how the randomized controlled trial, designed and promoted on the basis of its objectivity, rather than simply isolating the placebo effect, shaped drug treatment as a purely biological process. Just as Jeremy Greene has argued that chronic diseases such as hypertension were defined as such partly in relation to the introduction of drugs to treat them, the notion of drug efficacy was influenced by the method of action of the most effective drugs of the time.[14] This had the unforseen effect of limiting the way that drugs were used.

11. Daniel Carpenter, *Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA* (Princeton: Princeton University Press, 2010); Arthur A. Daemmrich, *Pharmacopolitics: Drug Regulation in the United States and Germany* (Chapel Hill: The University of North Carolina Press, 2004); Harry M. Marks, *The Progress of Experiment: Science and Therapeutic Reform in the United States, 1900–1990* (Cambridge: Cambridge University Press, 1997).

12. David Healy, *The Antidepressant Era* (Cambridge, Massachusetts: Harvard University Press, 1997).

13. Edward Shorter, *Before Prozac: The Troubled History of Mood Disorders in Psychiatry* (New York: Oxford University Press, 2009). Although proof of efficacy through controlled trials is required to license a new drug, only comparison with placebo is needed; therefore, new drugs are not necessarily more effective than older. However, as new drugs are under patent protection, and are thus more profitable for pharmaceutical companies, they are marketed heavily to practitioners, eclipsing older remedies.

14. Jeremy A. Greene, *Prescribing by Numbers: Drugs and the Definition of Disease* (Baltimore: The Johns Hopkins University Press, 2007).

THE DRUG AMENDMENTS OF 1962, CONTROLLED TRIALS AND LSD PSYCHOTHERAPY

The Drug Amendments of 1962 did not introduce the issue of efficacy to the FDA. Historians John Swann and Daniel Carpenter have effectively argued that although proof of efficacy was not required by the 1938 Food, Drug and Cosmetic Act, the FDA believed that efficacy was inextricably linked to safety and therefore considered it as part of the safety data necessary for licensing.[15] Nor did the Amendments introduce the issue of controlled trials to drug researchers. Control techniques had been developing in earnest since the 1930s and academic researchers in the 1950s increasingly espoused them as a way of bringing scientific standards to the newly burgeoning field of pharmacology.[16] The Amendments did, however, establish a new regime for drug development that made these two previously subsidiary matters central requirements for research. How these two requirements would be enforced, however, was not clear from the legislation, as they were couched in subjective terms: "Substantial evidence" of efficacy was required, consisting of "adequate and well-controlled investigations . . . by experts qualified . . . to evaluate the effectiveness of the drug involved."[17] Therefore, it is necessary to interrogate how the FDA, and experts, could interpret these terms in order to determine the influence of the Drug Amendments of 1962 on LSD research.

15. See Carpenter, *Reputation and Power*, 150–56; and John P. Swann, "Sure Cure: Public Policy on Drug Efficacy before 1962," in *The Inside Story of Medicines: A Symposium*, ed. Gregory J. Higby and Elaine C. Stroud (Madison, Wisconsin: American Institute of the History of Pharmacy, 1997), 223–61.

16. The history of the controlled trial has been traced back much further than the 1930s; however, this was when the various elements, such as comparative controls, blinding, placebos, and randomization, were combined to create a more formalized methodology. See Ted J. Kaptchuk, "Intentional Ignorance: A History of Blind Assessment and Placebo Controls in Medicine," *Bull. Hist. Med.*, 1998, *72*, 389–433; Abraham M. Lilienfeld, "Ceteris Paribus: The Evolution of the Clinical Trial," *Bull. Hist. Med.*, 1982, *56*, 1–18; Marks, *The Progress of Experiment*; J. Rosser Matthews, *Quantification and the Quest for Medical Certainty* (Princeton: Princeton University Press, 1995); Scott H. Podolsky, *Pneumonia before Antibiotics: Therapeutic Evolution and Evaluation in Twentieth-Century America* (Baltimore: The Johns Hopkins University Press, 2006); Arthur K. Shapiro and Elaine Shapiro, *The Powerful Placebo: From Ancient Priest to Modern Physician* (Baltimore: The Johns Hopkins University Press, 1997). For the increasing promotion of the controlled trial in the 1950s, see Harry M. Marks, "Trust and Mistrust in the Marketplace: Statistics and Clinical Research, 1945–1960," *Hist. Sci.*, 2000, *38*, 343–55; Scott H. Podolsky, "Antibiotics and the Social History of the Controlled Clinical Trial, 1950–1970," *J. Hist. Med. Allied Sci.*, 2010, *65*, 327–67.

17. *Drug Amendments of 1962*, Title 1, Part A, Sec. 102 (c).

Although the FDA did not provide an official elaboration of what constituted "adequate and well-controlled investigations" until 1970, in the years immediately following the legislation, interpretations provided by agency officials showed a clear preference for double-blind placebo-controlled trials, with a concession that they were not always possible. For example, in 1964, FDA Medical Director Joseph Sadusk stated, "Obviously, many experimental factors must be controlled. . . . This is preferably done by placebo comparisons in well-designed double-blind clinical studies." However, he emphasized that, "this is not the only type of study that can be called well-controlled."[18] When double-blind studies were not possible, the FDA would weigh the adequacy of a trial on factors such as its design, the expertise of the investigator, the methods used to record and assess results, and the nature of, and status of knowledge on, the disease being treated. Ultimately, as Carpenter has argued, Sadusk suggested that the term "adequate and well-controlled" was a descriptor given to a trial based on the subjective evaluation of the FDA, rather than a standard defined by protocols that a researcher could check off when designing a trial.[19] The double-blind placebo-controlled trial was the surest way of satisfying the FDA's standards, but every trial would be judged on a case-by-case basis, in light of expert opinion on the adequacy of the research methods for the drug and disease in question.

By the middle of the 1950s, expert opinion in pharmacology also favored the double-blind controlled trial, which was well established, at least in theory. In 1956, a major conference was held on the evaluation of psychiatric drugs. Sponsored by the National Institute of Mental Health, the National Academy of Sciences–National Research Council, and the American Psychiatric Association, the conference gathered

18. Joseph F. Sadusk, "The Definition of the Efficacy of a Drug under the Law," Symposium on Drug Investigation and Therapy, at the Second Fall Meeting of the American College of Physicians, Los Angeles, 8 October 1964, *Speeches and Papers, 1964* (Rockville, Maryland: Food and Drug Administration, 1979), FDA Biosciences Library, Silver Spring, Maryland. This position was also expressed in "Proceedings, FDA Conference on the Kefauver-Harris Drug Amendments and Proposed Regulations, February 15, 1963," FDA–Methodologies Used since New Drug Laws 1961–69, Box 6, MS C 372, Harry F. Dowling Papers, Modern Manuscripts Collection, History of Medicine Division, National Library of Medicine, Bethesda, Maryland, 25–26. For the later legislative elaboration, see Charles C. Edwards, "Hearing Regulations and Regulations Describing Scientific Content of Adequate and Well-Controlled Clinical Investigations," *Federal Register*, 8 May 1970, *35*, 7250–53.

19. Carpenter, *Reputation and Power*, 273.

together the nation's leading authorities on pharmacology and psychopharmacology and attracted a crowd of nearly 1,000, generating proceedings that can be seen as a representative of expert opinion. The majority of the participants supported the need for objective, standardized, and statistically driven clinical trials to determine the efficacy of drugs: as participants Johns Hopkins pharmacologists Louis Lasagna and Victor Laties commented, "Placebo and double-blind controls are of proven value in experimental work, and the reasons for their use should not need to be discussed at length in the year 1956."[20] Reflecting this opinion, the conference was concerned with a detailed analysis of the problems involved in trying to put the ideals into practice, rather than with justifying the techniques. Some attendees expressed doubts regarding the superiority and universal suitability of controlled trial techniques, but their concerns were quickly dismissed by the conference leadership.[21]

Despite the strong insistence on randomized controlled trials among elite researchers, with no concrete regulation over the conduct and standards of clinical research prior to 1962, adopting the complex and expensive methods of research remained voluntary. There existed, therefore, a great division between the theoretical state of the art and the common practice of clinical drug research, particularly in psychiatry. As University of Utah pharmacologist Louis Goodman commented, this led to a situation where drugs came to market on the back of poorly conducted clinical trials and "really good, definitive, critical, convincing, and properly controlled clinical studies are published only years after the drug has made the grade or has begun its well-deserved disappearance from the therapeutic scene."[22] This situation is clearly evident in the case of chlorpromazine, the first antipsychotic drug, considered by many to be the greatest drug breakthrough for psychiatry. At the time of its FDA approval in 1954, only uncontrolled studies of its psychiatric effects had been reported, and proof of efficacy

20. Louis Lasagna and Victor G. Laties, "Problems Involved in the Study of Drug-Modified Behavior in Normal Humans," in *Psychopharmacology: Problems in Evaluation*, ed. Jonathan O. Cole and Ralph W. Gerard (Washington, DC: National Academy of Sciences–National Research Council, 1959), 89.

21. For critiques of the randomized controlled trial, and rebuttals, see ibid., 327–28, 605, 615, 624–26.

22. Ibid., 589.

from a well-controlled trial did not appear until 1960.[23] Interestingly, the most highly controlled trial reported in the 1950s gave negative results, yet did not appear to impact the drug's uptake: within eight months of being marketed, it had been given to two million patients, and had increased the firm's sales by one-third within a year.[24]

At the time of the passage of the Drug Amendments of 1962, both the FDA and experts had a strong preference for randomized controlled trials wherever possible. The great significance of the Amendments was not the introduction of the issues of efficacy or controlled clinical trials, but that those who were strong supporters of the methodology were given authority over the conduct of research. Therefore, although regulators may not have been fairly able to expect the randomized double-blind controlled trial to be fully realized in all clinical research by 1962, it was certainly the preeminent model on which to evaluate the quality of research. On this basis, it can reasonably be concluded that an "adequate and well-controlled trial" could be considered the one that made a concerted attempt to address issues such as bias, the placebo effect, influencing variables, chance, and natural variation in disease, through techniques such as randomization, double-blind placebo comparison, standardized treatment, environments and measures, and statistical analysis. While the FDA and researchers alike saw this methodology as simply the most accurate and scientifically advanced, it carried with it assumptions that clashed with LSD psychotherapy's unique method of treatment, frustrating the progress of

23. For an example of the uncontrolled research, see N. W. Winkelman, Jr., "Chlorpromazine in the Treatment Neuropsychiatric Disorders," *J. Am. Med. Assoc.*, 1954, *155,* 18–21. For the later controlled trial, see Jesse F. Casey et al., "Drug Therapy in Schizophrenia: A Controlled Study of the Relative Effectiveness of Chlorpromazine, Promazine, Phenobarbital, and Placebo," *Am. Med. Assoc. Arch. Gen. Psych.,* 1960, *2*, 210–20.

24. Robert A. Hall and Dorothy J. Dunlap, "A Study of Chlorpromazine: Methodology and Results with Chronic Semi-Disturbed Schizophrenics," *J. Nerv. Ment. Dis.,* 1955, *122*, 301–14. For chlorpromazine's reception, see Judith P. Swazey, *Chlorpromazine in Psychiatry: A Study of Therapeutic Innovation* (Cambridge, Massachusetts: The MIT Press, 1974), 160–61; Healy, *The Creation of Psychopharmacology* (Cambridge, Massachusetts: Harvard University Press, 2002), 99–100. The minor tranquilizer meprobamate and antidepressant iproniazid, developed in the same period, were similarly approved on the basis on uncontrolled research. See Andrea Tone, *The Age of Anxiety: A History of America's Turbulent Affair with Tranquilizers* (New York: Basic Books, 2009), 48–49; Joseph C. Borrus, "Study of Effect of Miltown (2-Methyl-2-*N*-Propyl-1,3-Propanediol Dicarbamate) on Psychiatric States," *J. Am. Med. Assoc.,* 1955, *157*, 1596–98; Harry P. Loomer, John C. Saunders, and Nathan S. Kline, "A Clinical and Pharmacodynamic Evaluation of Iproniazid as a Psychic Energizer," *Psychiatr. Res. Rep.*, 1957, *8,* 129–30.

research, and, more broadly, furthered the division between psychiatry's pharmaceutical and psychological treatments.

Randomized double-blind controlled trials were ideal for testing "magic bullet" type drugs, such as antibiotics, that targeted a specific illness through a direct action in the body or brain. This form of drug efficacy allowed the easy use of placebos, double-blinding, and standardized treatment, as it involved simply administering a medication. Indeed, the history of the randomized controlled trial has been strongly linked with antibiotics, as historians have frequently pointed to the 1940s streptomycin research of Austin Bradford Hill in Britain as the most influential in the development of the modern randomized controlled trial.[25] Scott Podolsky has further argued that the increasing promotion of the methodology in the 1950s was influenced by the influx of new antibiotics that needed accurate evaluation and differentiation.[26] The dramatic success of the antibiotics, discovered in the 1930s and 1940s, provided the realization of an ideal magic bullet form of drug effect that had long been theorized.[27] With these miracle drugs' efficacy deriving from an objective biological action, and the most advanced method of testing drug efficacy best suited to these kinds of drugs, the assumption followed that this was the most legitimate form of drug action. The breakthrough psychiatric drugs of the 1950s largely conformed to this magic bullet theory of drug efficacy—the new antipsychotics, antidepressants, and anxiolytics worked regardless of the treatment environment or the interpersonal skill of the physician. The main issues in pharmacotherapy became simply fitting a diagnosis to a medication.

For LSD psychotherapists, the promotion of the double-blind controlled trial, and the assumptions inherent in it, made providing proof of efficacy extremely difficult. LSD was used merely as a tool in a psychotherapeutic treatment—a catalyst for attaining states of consciousness or experiences that could be used by a skilled therapist to therapeutic ends. The drug had no inherent beneficial effects; instead, its efficacy lay in the psychological impact of the subjective drug

25. See Daemmrich, *Pharmacopolitics*, 51; Healy, *The Antidepressant Era*, 89; Lilienfeld, "Ceteris Paribus," 17; Mark Parascandola, "Clinical Testing: New Developments and Old Problems," in *The Inside Story of Medicines*, ed. Higby and Stroud, 201.

26. Podolsky, "Antibiotics," 327–67.

27. See Robert Bud, *Penicillin: Triumph and Tragedy* (Oxford: Oxford University Press, 2007), 14–18.

experience, which was crafted through a unique relationship between the patient, therapist, and drug. This complex web of extrapharmacological factors was very difficult to replicate in a blind control group, as was required to prove that results were due to the use of the drug. Added to this was the simple practical difficulty of designing a trial with LSD that could sustain a double-blind process. The dramatic psychoactive effects of LSD meant that any use of an inert placebo as a control would be useless; the blind would disappear as soon as the LSD took effect. Therefore, a successful double-blind study would require an active placebo that would mimic all the symptoms of LSD intoxication, yet lacked its therapeutic qualities. No such drug existed, and the possibility of one was theoretically complicated: many of the subjective effects that the active placebo would have to mimic were the aspects that were therapeutically useful.[28]

These difficulties formed part of a broader problem facing LSD researchers. Because LSD psychotherapy utilized a drug, it came under the regulation of the FDA, and thus needed to provide proof of efficacy in the same manner as any other drug treatment. However, LSD psychotherapy was not a drug therapy, but instead a psychotherapy. The double-blind controlled trial was not designed to test the efficacy of psychotherapies, which was a much more complicated task: researchers had to confront issues such as the lack of consensus on specific etiological theory or therapeutic method; the wide variety of conditions treated by any one psychotherapy; the varying goals of treatment; the contention that the need to control psychological factors was not relevant as psychotherapy itself was a psychological treatment; and the difficulty of designing control treatments and "blinding" therapists.[29] Where controlled trials were attempted, they varied widely in their design and provided little clarity on the specific efficacies of treatments.[30] The difficulties in evaluating effectiveness were exacerbated by the skepticism of

28. Hoffer, "A Program for the Treatment of Alcoholism," 365; Robert E. Mogar, "Research in Psychedelic Drug Therapy: A Critical Analysis," in *Research in Psychiatry: Proceedings of the Third Conference,* ed. John M. Shlien (Washington, DC: American Psychological Association, 1968), 500–11; Richard Yensen, "LSD and Psychotherapy," *J. Psychoactive Drugs*, 1985, *17*, 267–77, 273.

29. See Jerome D. Frank, *Persuasion and Healing: A Comparative Study of Psychotherapy* (New York: Schocken Books, 1963), 20–22; Shapiro and Shapiro, *The Powerful Placebo*, 96–122.

30. Lester Lubrosky, Barton Singer, and Lise Lubrosky, "Comparative Studies of Psychotherapies: Is It True That 'Everyone Has Won and All Must Have Prizes'?" *Arch. Gen. Psych.,* 1975, *32*, 995–1008.

therapists toward the possibility of such research. Psychoanalysts were particularly hostile, arguing that research methods were ill-equipped to evaluate the complexities of their treatment.[31] The reality was that all research was purely academic as psychotherapies did not need to prove their efficacy in order to be practiced: "talk therapies" did not involve any physically invasive procedures, making them of little interest to federal regulators and outside the jurisdiction of the FDA.

Whether or not the FDA directly pressured LSD psychotherapy researchers to use randomized controlled trials is not clear. The FDA had acknowledged that the methodology could not always be applied. However, as will be explored, it is clear that LSD researchers felt the need to adopt controlled trials in order to provide convincing proof of effectiveness. Available evidence strongly suggests that the FDA would accept nothing less than evidence from sophisticated controlled trials to support LSD's efficacy. In 1966, FDA commissioner James Goddard appeared before three congressional hearings investigating aspects of LSD's regulation. Although the hearings focused on LSD's growing recreational use, medical research was also discussed and was treated as an entirely separate issue. In all three hearings, Goddard criticized LSD psychotherapy research on the grounds of poor methodology, concluding that there was no proof of efficacy. Indeed, he even claimed that "there is as yet no substantial evidence based on adequate and well controlled investigations to support the use of [LSD] for any medical purpose,"—terms lifted directly from the Drug Amendments of 1962.[32] Further, he described the available data on LSD as "very crude" and, when asked why there was no consensus on the drug's efficacy after ten years of research, replied that difficulty in finding an active placebo that would allow double-blind testing was a "problem that has confounded much of the research up to now."[33] Stanley Yolles, Director of the National Institute of

31. Nathan G. Hale, Jr., "American Psychoanalysis since World War II," in *American Psychiatry after World War II (1944–1994)*, ed. Roy W. Menninger and John C. Nemiah (Washington, DC: American Psychiatric Press, 2000), 77–102, 91; Edward Shorter, *A History of Psychiatry: From the Era of the Asylum to the Age of Prozac* (New York: John Wiley & Sons, 1997), 311.

32. House Subcommittee of the Committee on Government Operations, *Drug Safety (Part 5, Appendixes, and Index)*, 89th Congress, 2nd Session, 9–10 March, 25–26 May, 7–9 June 1966 (Washington: U.S. Government Printing Office, 1966), 2135.

33. *Organization and Coordination: LSD,* 59; *The Narcotic Rehabilitation Act of 1966,* Hearings before a Special Subcommittee of the Committee on the Judiciary, U.S. Senate, 89th Congress, 2nd Session, 25–27 January, 12, 13, 19, 23, and 25 May, 14 and 15 June, 19 July 1966 (Washington: U.S. Government Printing Office, 1966), 345.

Mental Health, which worked closely with the FDA, stated that LSD use needed to be strictly restricted to "carefully controlled experiments until *incontrovertible* data are available documenting LSD's efficacy and safety."[34] The distinct change in research methods employed by the LSD researchers before and after the Drug Amendments of 1962 also itself strongly suggests that the passage of the legislation made clear to researchers the need to employ controlled trials.

LSD psychotherapy researchers were therefore in a unique and difficult position. They were the first researchers required to provide proof of efficacy for a form of psychotherapy, and at a time when there was no consensus on an accurate method for doing so.

EVALUATING EFFICACY: PSYCHEDELIC THERAPY RESEARCH AFTER 1962

Prior to 1962, research with LSD primarily consisted of close empirical studies on small numbers of patients. There was frequently no control group, although as patients chosen for the studies were often severely ill and considered treatment resistant, any improvement was considered significant. The patients in a trial often had a variety of diagnoses—ranging from neuroses, to schizophrenia, to alcoholism—and researchers judged the effect of the treatment by subjective evaluations. They focused on closely monitoring and analyzing the effect that the drug had on the individual patients, with reports often including long transcripts from LSD sessions, discussion of the psychodynamic relevance of the material, and how it differed from their drug-free sessions.[35] Prior to 1962, this kind of research was methodologically in line with the standard practice of pharmaceutical research. However, after 1962, it came under increasing scrutiny.

After 1962, LSD researchers changed their focus to the scientific rigor of their clinical trial design, often to the detriment of their therapeutic method. This trend can be demonstrated through an analysis of

34. Ibid., 33. Emphasis mine. The quote was originally from the New York County Medical Society; Yolles reproduced it as a representation of the NIMH's view.

35. For examples, see Harold A. Abramson, "Lysergic Acid Diethylamide (LSD-25): III. As an Adjunct to Psychotherapy with Elimination of Fear of Homosexuality," *J. Psychol.*, 1955, *39*, 127–55; Betty Grover Eisner and Sidney Cohen, "Psychotherapy with Lysergic Acid Diethylamide," *J. Nerv. Ment. Dis.*, 1958, *127*, 528–39; Hoffer, "A Program for the Treatment of Alcoholism," 343–75; Sherwood et al. "The Psychedelic Experience," 69–80.

the four clinical trials for therapeutic research with LSD funded by the National Institute of Mental Health, between 1963 and 1968.[36] All were prompted by the reports of dramatic recovery amongst alcoholics following psychedelic therapy. While intrigued by these results, the researchers were all highly critical of the uncontrolled research that had produced them, and therefore decided to put the treatment under scientific examination. However, in doing so, three of the four studies ignored many of the fundamental features of psychedelic therapy that the developers of the treatment had considered key to its success. These three studies all reported negative results for LSD's efficacy, while the fourth trial, which utilized the therapeutic method developed by Hoffer, Osmond, and Hubbard, reported a more positive outcome.

Two of the studies explicitly displayed a focus on trial design over therapeutic method, to the extent that their tested treatments involved no psychotherapy. The first was performed by Leo Hollister and colleagues at the Veterans Administration Hospital in Palo Alto, California. Hollister had become a prominent researcher in the early 1960s by demonstrating that the "model psychosis" produced by LSD and similar drugs was in fact distinctly different from schizophrenia, undermining the value of research using the drugs to study psychoses.[37] Regarding LSD psychotherapy, Hollister stated that "not one single report . . . meets the criteria for an adequate evaluation by modern standards of clinical pharmacology," due to the "absence of controls or random assignment to comparison treatment, failure to use blind techniques, failure to account for nonspecific factors in treatment programs, and inadequate follow-up procedures."[38] He maintained a skeptical attitude toward not only LSD but the psychotherapeutic forms which it facilitated, such as abreactive or group therapy. Nevertheless, he argued that methodologically sound studies of LSD psychotherapy were possible.[39]

36. A table of NIMH grants for "Hallucinogenic Study" for 1953 projected up to 1968 is included in *Organization and Coordination: LSD*, 18–25.

37. Leo E. Hollister, "Drug-Induced Psychoses and Schizophrenic Reactions: A Critical Comparison," *Ann. N. Y. Acad. Sci.*, 1962, *96*, 80–93.

38. Leo E. Hollister, *Chemical Psychoses: LSD and Related Drugs* (Springfield, Illinois: Charles C. Thomas, 1968), 123; Leo Hollister, Jack Shelton, and George Krieger, "A Controlled Comparison of Lysergic Acid Diethylamide (LSD) and Dextroamphetamine in Alcoholics," *Am. J. Psychiatry*, 1969, *125*, 1352.

39. Hollister, *Chemical Psychoses,* 123–42.

However, in attempting to substantiate this claim, Hollister adopted a "medical" model of treatment that assumed any beneficial effects of LSD were inherent in the drug's action. Seventy-two alcoholics were treated in his randomized double-blind trial, which compared a large dose of LSD against the stimulant dextroamphetamine as an active placebo. The treatment consisted of merely administering the drugs in a comfortable room and giving the patient brief reassurance when needed. Rather than the extensive preparation typical of psychedelic therapy, prior to treatment, the patient simply had a discussion with their psychiatrist regarding their drinking problem, designed to minimize guilt over their condition, and were encouraged to use the drug session for self-examination. At no point was psychotherapy given. Specific preparation for receiving LSD was also almost nonexistent: as Hollister wrote "Within the bounds of medical ethics, patients were given as little concrete information as possible about the drugs to be tested." In fact, they were not even named. The results of the study were, unsurprisingly, negative.[40]

Keith Ditman had been researching LSD at the University of California, Los Angeles since the mid-1950s. His earliest study was a comparison of the effects of LSD with the experience of delirium tremens, which found significant differences.[41] Despite this study not being a therapeutic trial, many of the subjects given LSD reported beneficial effects.[42] As well as this research, throughout the 1960s, Ditman published critiques of LSD psychotherapy research, highlighting the lack of controlled trials, and studied the harmful effects of the nonmedical use of LSD.[43] Ditman's LSD and alcoholism trial, reported in 1969, paid some attention to set and setting, with the experiment taking place in an "LSD setting," although the exact nature of this setting was not explained. In the double-blind experiment, all patients were expecting to receive LSD, but some instead received the stimulant methylphenidate, or the minor tranquilizer chlordiazepoxide. Results

40. Hollister, Shelton, and Krieger, "A Controlled Comparison," 1352–57.

41. Keith S. Ditman and John R. B. Whittlesey, "Comparison of the LSD-25 Experience and Delirium Tremens," *Am. Med. Assoc. Arch. Gen. Psych.*, 1959, *1*, 47–57.

42. Keith S. Ditman, Max Hayman, and John R. B. Whittlesey, "Nature and Frequency of Claims Following LSD," *J. Nerv. Ment. Dis.*, 1962, *134*, 346–52.

43. See Keith S. Ditman, "The Value of LSD in Psychotherapy," in *The Problems and Prospects of LSD*, ed. J. Thomas Ungerleider (Springfield, Illinois: Charles C Thomas, 1968), 45–60; and Keith S. Ditman et al., "Harmful Aspects of the LSD Experience," *J. Nerv. Ment. Dis.*, 1967, *145*, 464–74.

were not measured in terms of the treatments' effects on long-term drinking behavior, but on an analysis of patients' drug sessions for the prevalence of experiences usually deemed therapeutic, such as increased self-understanding. The study found LSD to be no more therapeutic than the two control drugs.[44] Although patients were slightly better prepared in this study, the lack of any psychotherapy still precludes any real comparison with psychedelic therapy.

The two other studies did involve psychotherapy, but a thorough analysis of their theoretical frameworks, therapeutic methods, and results reveals that the attempt to design a scientifically rigorous clinical trial could obscure rather than clarify psychedelic therapy's efficacy in treating alcoholism. At the Mendota State Hospital in Wisconsin, Arnold Ludwig, Jerome Levine, and Louis Stark led a clinical trial of LSD in the treatment of alcoholism that was probably the most sophisticated ever designed. Although their trial utilized psychotherapy, the method of treatment they tested still differed significantly from the psychedelic therapy paradigm established by Hoffer, Osmond, and their colleagues. For the trial, the Wisconsin researchers invented a new and unique LSD therapy, which under scrutiny showed negative results.

Ludwig and Levine had first begun working with LSD at the Federal Hospital for narcotic drug addicts at Lexington, Kentucky, in 1962. There they developed a treatment combining LSD with hypnosis—"hypnodelic therapy"—to treat narcotics addicts, and later, alcoholics. Their impetus for investigating LSD came from frustration at the ineffectiveness of the hospital's normal psychotherapeutic treatment, and anecdotal reports from colleagues that a few patients who had been given the drug in a nontherapeutic experiment had claimed the experience changed their outlook on life and values in a positive direction, away from drugs.[45] The results of a pilot study, reported in 1965, were positive; therefore, Ludwig and Levine decided to undertake a larger scale study of the efficacy of LSD in treating chronic alcoholism.[46] They were highly critical of previous research in this area, stating that

44. Keith S. Ditman et al., "Dimensions of the LSD, Methylphenidate and Chlordiazepoxide Experiences," *Psychopharmacologia*, 1969, *14*, 1–11.

45. Arnold M. Ludwig and Jerome Levine, "Hypnodelic Therapy," *Curr. Psychiatr. Ther.*, 1967, *7*, 130–41, 130–31.

46. Arnold M. Ludwig and Jerome Levine, "A Controlled Comparison of Five Brief Treatment Techniques Employing LSD, Hypnosis, and Psychotherapy," *Am. J. Psychother.*, 1965, *19*, 417–35.

"therapeutic claims for this drug have been more of the nature of religious testimonials or statements of clinical conviction than cautious scientific observations and interpretations." Therefore, they set out to right the wrongs of previous research. The stakes were high as "If the glowing claims for LSD could be substantiated, the drug would indeed revolutionize psychiatric treatment," but the "proof will only be forthcoming through an impartial arbiter, known as *scientific method,* which makes no compromise with bias, regardless of its source."[47]

The study took place in the Alcoholic Treatment Center of the Mendota State Hospital over four years, with results published in 1970. A total of 176 male patients took part in the study. The researchers reasonably concluded that a double-blind trial was impractical with LSD, so decided on a controlled comparison method. Patients were randomly assigned to one of four treatments, with an equal number of patients in each treatment; half of each treatment group was also randomly assigned to receive Antabuse on discharge, a drug that causes severe nausea when ingested with alcohol. Psychiatrists were given an equal number of patients from each treatment group.[48] In lieu of the double-blind, the researchers attempted to minimize a bias toward the experimental treatments by withholding information regarding the nature of the trial. Patients were told, before volunteering, that they would receive one of four treatments involving, either alone or in combination, LSD, hypnosis, a "contemplative session" and Antabuse; however, they were not told that it was an experimental comparison, but instead that the most appropriate treatment for their condition would be chosen. Only basic information regarding LSD was given and neither the patient nor psychiatrist knew which treatment was going to be used until just prior to the session.[49] Thirteen psychiatrists administered the treatments, seven of whom were second- or third-year psychiatric residents. All were volunteers who were trained in hypnosis and LSD administration by Ludwig through "extensive reading material" and "demonstration sessions."[50]

47. Arnold M. Ludwig, Jerome Levine, and Louis H. Stark, *LSD and Alcoholism: A Clinical Study of Treatment Efficacy* (Springfield, Illinois: Charles C. Thomas, 1970), 19, 25.

48. Arnold M. Ludwig et al., "A Clinical Study of LSD Treatment in Alcoholism," *Am. J. Psychiatry,* 1969, *126*, 59–69, 62. Antabuse is the trade name for disulfiram, a drug that causes the intake of alcohol to produce extremely unpleasant effects such as vomiting and headaches.

49. Ludwig et al., *LSD and Alcoholism*, 74–76, 87.

50. Ibid., 80.

The four tested treatments were hypnodelic therapy, psychedelic therapy, drug therapy, and milieu therapy. Both the hypnodelic therapy and psychedelic therapy treatments involved LSD and psychotherapy, but they had little in common with the psychedelic therapy methods established in the 1950s, which focused on attaining the psychedelic experience through the manipulation of the patient's "set and setting" by the therapist, who acted as a supportive guide throughout the entirety of the drug's period of action. In fact, when developing hypnodelic therapy, Ludwig had thought that hypnosis could be a good tool for directing the LSD experience toward outlook and value changes while minimizing the distractions of hallucinations and "nirvana-like feelings."[51]

Hypnodelic therapy involved hypnotizing the patient in the period between LSD administration and the onset of its effects, during which a strong bond with the therapist was established, and suggestions were given that the treatment provided a new chance for insight and improvement. Once the drug was in effect, a two-hour therapy session was conducted along the lines of conventional dynamic psychotherapy, but with increased depth, suggestibility, and intensity. Emphasis was placed on recalling and reliving past traumatic events, and comprehending negative dynamic processes. After the session, the hypnotic trance was lifted and the patient was put into an overnight room where alone, except for periodic checks by a nurse, he was encouraged to use the rest of the drug's action (another eight to ten hours) to further think through the issues discussed during the session and possibly write up the experience.[52]

The Wisconsin researchers' form of psychedelic therapy was essentially the same as hypnodelic therapy, but without hypnosis: LSD plus conventional psychotherapy focusing on the patients' major problems. Drug therapy was the administration of LSD without psychotherapy. Milieu therapy involved no drugs or psychotherapy, but a period of "contemplation and meditation" alone, where the patient was told to think hard about their problems and make plans for the future—this was the primary control group. Prior to all treatments, patients went through a two-hour psychiatric interview with their assigned therapist in order to gather personal information on which to base any psychotherapy.

51. Ludwig and Levine, "Hypnodelic Therapy," 130–31.
52. Ibid., 134–35.

This brief preparation contrasts significantly with the established technique of psychedelic therapy, where weeks of psychotherapy prepared the patient for the drug session. All treatments lasted three hours, after which the patient was placed in an observation room overnight. The dose of LSD for the three drug treatments was three micrograms per kilogram of body weight.[53]

The most impressive aspect of Ludwig, Levine, and Stark's clinical trial was in the method of determining results. Patient evaluations were performed by social workers that were blinded to the patient's treatment group. They assessed patients with a battery of tests—a total of five used in different combinations at different times—prior to the first therapist meeting, prior to discharge, then at three, six, nine, and twelve months after discharge. The tests rated patients on aspects of personality, psychological health, drinking behavior, and social adjustment. A relative was also interviewed prior to treatment and six and twelve months later.[54] The data from the follow-up assessments were analyzed extensively to determine any statistical significance in improvement rates between the four treatments. Analysis was also performed to determine whether certain variables could influence the outcome: the patients' marital status, age, whether or not their therapist had finished residency, motivation for improvement, pretreatment personality assessment, and the subjective report of their LSD experience.

Ludwig, Levine, and Stark concluded that although all four treatment groups showed improvement in most areas of assessment, none of the LSD treatments produced significantly different results than the control treatment. Variables analyzed seemed to have no impact on results. Antabuse was also judged as ineffective.[55] The researchers were confident enough in their methodology and the comprehensiveness of their study to state that their negative results produced such "inescapable conclusions about the purported efficacy of LSD for the treatment of alcoholism as to preclude any further investigation, at least as far as evaluating the usefulness of the particular techniques used in this study."[56]

The research led by Albert Kurland at the Spring Grove State Hospital, Maryland, contrasts significantly with that of Ludwig and his

53. Ludwig et al., *LSD and Alcoholism*, 87–89.
54. Ibid., 81, 90–96.
55. Ibid., 128–45.
56. Ibid., 9.

colleagues in theory, therapeutic method, scientific design, and results.[57] Kurland and his team researched several applications for LSD psychotherapy: research into the efficacy of the LSD in the treatment of alcoholics was their major study as well the one comparable to other research. In regard to their therapeutic method and its theoretical basis, their work was a direct continuation and development of the earlier Canadian research. Kurland led a large group of researchers, many of whom had long independent histories of LSD research in a number of areas. Charles Savage had been one of the first in the United States to investigate the therapeutic potential of hallucinogens, beginning in 1949, and his research continued uninterrupted into the early 1970s. His career with the drugs was perhaps the longest and most extensive of any U.S. researcher: he began studying LSD as an adjunct in psychoanalytically orientated psychotherapy (psycholytic therapy), and became a key figure in developing psychedelic therapy in the United States.[58] Stanislav Grof, from Czechoslovakia, was one of Europe's most prominent and experienced LSD researchers, beginning in 1956 and by 1968 reporting presence at 1,100 LSD and psilocybin sessions.[59] Walter Pahnke was also well known in his own right, especially for a study known as the "Good Friday experiment" or "The Miracle of Marsh Chapel," in which the administration of psilocybin generated intense religious experiences among a group of divinity students. With a medical degree already behind him, Pahnke's experiment investigated the "relationship between psychedelic experience and the mystical state of consciousness" for his Ph.D. at Harvard Divinity School in 1962.[60]

57. In 1969, the research team moved to the new Maryland Psychiatric Research Center on the hospital's grounds. For more on the history of psychedelic research at these institutions, see Richard Yensen and Donna Dryer, "Thirty Years of Psychedelic Research: The Spring Grove Experiment and Its Sequels," *Jahrbuch des Europäischen Collegiums für Bewußtseinsstudien/ Yearbook of the European College for the Study of Consciousness*, 1993–94, 73–102.

58. *Drug Safety*, 2212. For his psycholytic research, see Charles Savage, "Lysergic Acid Diethylamide (LSD-25): A Clinical–Psychological Study," *Am. J. Psychiatry*, 1952, *108*, 896–900; and Charles Savage, "The LSD Psychosis as Transaction between the Psychiatrist and Patient," in *Lysergic Acid Diethylamide and Mescaline in Experimental Psychiatry*, ed. Louis Cholden (New York and London: Grune & Stratton, 1956), 35–43. For his early psychedelic research, see Savage, "LSD, Alcoholism and Transcendence," 429–35.

59. Stanislav Grof, *LSD Psychotherapy* (Pomona: Hunter House, 1980), 13; Stanislav Grof, "Tentative Theoretical Framework for Understanding Dynamics of LSD Psychotherapy," in *Research in Psychotherapy*, ed. Shlien, 449–65, 449.

60. Walter N. Pahnke, "Drugs & Mysticism: An Analysis of the Relationship between Psychedelic Drugs and Mystical Consciousness" (PhD diss., Harvard University, 1963), i. Kurland's first research with LSD was in a study of its effect on schizophrenics: Louis

In a similar way to Ludwig's research, planning for the Spring Grove studies began in 1963 under the pressure of increasing populations of alcoholic patients for whom there was no effective treatment, and an awareness of the positive reports of LSD therapy in treating the condition. A preliminary study was conducted to explore LSD's treatment potential and develop a therapeutic method.[61] Very promising results led to a large-scale clinical trial.

Significant attention needs to be placed on the Spring Grove team's therapeutic method and its theoretical basis, as this is what they argued determined efficacy, and was a major focus of their reports. The main tenet of their theory was that LSD did not "have any inherent beneficial effects."[62] Instead, the therapeutic benefit of LSD was tied up in the way the drug was used, that is, in the type of reaction the patient had to the drug and the way this reaction was utilized. The reaction the Spring Grove researchers deemed most therapeutic was the peak, or transcendental, reaction and they called their method "psychedelic-peak therapy." The team listed the basic characteristics of the psychedelic-peak reaction:

1) Sense of unity or oneness (positive ego transcendence, loss of usual sense of self without loss of consciousness).
2) Transcendence of time and space.
3) Deeply felt positive mood (joy, peace, and love).
4) Sense of awesomeness, reverence, and wonder.
5) Meaningfulness of psychological and/or philosophical insight.
6) Ineffability (sense of difficulty in communicating the experience by verbal description).[63]

The beneficial psychedelic-peak experience was reliably produced through careful manipulation of the mind-set of the patient and the setting in which he or she was administered LSD. Approximately twenty hours of preparatory psychotherapy carefully shaped the mind-set of

S. Cholden, Albert Kurland, and Charles Savage, "Clinical Reactions and Tolerance to LSD in Chronic Schizophrenia," *J. Nerv. Ment. Dis.*, 1955, *122*, 211–21.

61. Albert A. Kurland et al., "Psychedelic Therapy Utilizing LSD in the Treatment of the Alcoholic Patient: A Preliminary Report," *Am. J. Psychiatry*, 1967, *123*, 1202–9, 1202.

62. *Drug Safety*, 2213.

63. Albert Kurland et al., "LSD in the Treatment of Alcoholics," *Pharmakopsychiatrie-Neuro-Psychopharmakologie*, 1971, *4*, 83–94, 85.

the patient to help them achieve the psychedelic-peak experience, and bring them to a state where it could be of most use. "The LSD session can add meaningful emotional insight and dramatic validation of an individual's basic self-worth," the researchers argued, "but usually only after the achievement of psychodynamic resolution and self understanding during the preparatory psychotherapy."[64] The therapist and a psychiatric nurse stayed with the patient throughout the ten-to-twelve-hour LSD session. During the session, interaction between the therapist and the patient was not in the form of formal psychotherapy or analysis. Instead, the therapist was there to provide support, direct the patient's reaction toward beneficial insights and experiences, and for "mobilizing and integrating affective responses and dynamic material as the patient's experiences unfold."[65] The experience was "corrective and remedial" as opposed to uncovering, for "the psychedelic procedure is designed to program and guide the evolving episodes of experience so as to regularly achieve meaningful catharsis, reciprocal inhibition of anxiety, conflict resolution, emotionally validated insight, attitude redirection, elevated self-esteem, and deepened philosophical perspective."[66]

Just as the patient's mind-set was carefully directed toward attaining the peak experience, so too was the setting. Instead of a normal clinical setting, the drug session took place in a room made up like a "comfortable living room, with sofa, easy chairs, rugs, drapes, pictures, flowers, and high-fidelity music equipment."[67] Eyeshades and "carefully selected" classical music were used extensively throughout the session, heightening emotionality and drawing the patient deeper into their "inner world." Overall, the setting and therapist's role were designed to avoid a negative reaction to the drug and to direct the patient toward the peak experience, by making them feel safe and comfortable, encouraging them to "let go" and delve deeply into their minds, and providing beautiful and emotive stimulus. After the session, follow-up psychotherapy helped cement the positive insights and experiences

64. Walter N. Pahnke et al., "The Experimental Use of Psychedelic (LSD) Psychotherapy," in *Hallucinogenic Drug Research: Impact on Science and Society*, ed. James R. Zerkin and Edmund L. Gamage (Beloit, Wisconsin: STASH Press, 1970), 48–68, 51–53.

65. Kurland et al., "Psychedelic Therapy," 1206.

66. Sanford Unger et al., "LSD-Type Drugs and Psychedelic Therapy," in *Research in Psychotherapy*, ed. Shlien, 521–35, 522.

67. Kurland et al., "LSD in the Treatment of Alcoholics," 84.

into the patient's personality, ensuring lasting changes in their behavior and attitudes.[68]

The major alcoholic study at Spring Grove tested the efficacy of psychedelic-peak therapy on 117 patients of the hospital's Alcoholic Rehabilitation Unit, with results reported in 1971. The study was randomized and double-blind with the experimental group administered 450 micrograms of LSD, and the control receiving 50 micrograms. A control group utilizing a low dose of LSD as an active placebo was chosen as experience had proven it impossible to maintain the blind with an inert placebo. The low dose would manifest in the patients many of the symptoms, and some of the emotionality, of a high dose, but they would not experience the psychedelic-peak reaction. For evaluation, an independent team of social workers administered a battery of psychological tests before the treatment program began, one week after the LSD session, and then at six, twelve, and eighteen months. The follow-up assessments rated patients on drinking behavior and global adjustment (which included factors such as employment and interpersonal relationships).[69]

At the six-month follow-up point, the high-dose treatment group showed a statistically significant advantage over the low dose, with 53 percent of high-dose patients considered "essentially rehabilitated" compared with 33 percent of the low dose for drinking behavior. In terms of global adjustment, 44 percent of the high dose and 25 percent of the low-dose patients were considered "essentially rehabilitated." Results were still higher for the high-dose group at the twelve- and eighteen-month points but were not considered statistically significant.[70] The team also analyzed the results in relation to the subjective drug effects, labeled "psychedelic reactivity," regardless of dose, testing the hypothesis that it was the profound peak experience that was most therapeutically beneficial. The results were statistically significant, in favor of the more profound reactions, for global adjustment. Drinking behavior results displayed a similar trend though were not statistically significant.[71]

68. Pahnke et al., "The Experimental Use of Psychedelic (LSD) Psychotherapy," 52–53.

69. Kurland et al., "LSD in the Treatment of Alcoholics," 85–89; Charles Savage et al., "Research with Psychedelic Drugs," in *Psychedelic Drugs*, ed. Richard E. Hicks and Paul Jay Fink (New York: Grune & Stratton, 1969), 15–22, 17.

70. Kurland et al., "LSD in the Treatment of Alcoholics," 91. At eighteen months, results of essentially rehabilitated were 54 percent for the high dose and 47 percent for the low dose for drinking behavior, and 53 and 41 percent for global adjustment.

When the researchers reported the six-month results, they put forward a modest claim of efficacy: "in practical terms, we can say that a given alcoholic patient receiving a single high dose of LSD in the context of psychedelic-peak psychotherapy and experiencing a profound psychedelic-peak reaction has the best likelihood for improvement 6 months later."[72] When the eighteen-month results were collected, Kurland and colleagues presented arguments both for and against their significance, and offered cautious yet encouraging interpretations. Although results were statistically significant at six months, he expressed a desire for a greater level of significance for truly convincing results. He also suggested that a number of variables not equalized by randomization could have favored the high-dose group, although the strong improvement of both groups did not suggest that they had. The inclusion of a nondrug control group was now seen as a potential clarifier of results. Regardless of these difficulties in determining the efficacy of high versus low dose, the overall results of psychedelic therapy were interpreted by the Spring Grove team as very effective compared with the standard treatment procedure. A previous study of the standard therapy at the same institution, with comparable alcoholics, found a 12 percent recovery rate at eighteen months, compared with 54 percent at the same point in the LSD study. As impressive as this appeared, it was not part of the same study, so it could not be formally considered in determining proof of efficacy. Overall, they concluded that the "clinical achievements of only one psychedelic peak experience and its maintenance for a period of several months in these types of patients is an observation that cannot be discounted."[73] Further research was proposed in order to learn how to "sustain and maximize" these positive results.

DEBATING DESIGN: SCIENTIFIC RIGOR AND THERAPEUTIC METHOD

In 1971, Spring Grove researcher Charles Savage wrote a scathing review of Ludwig, Levine, and Stark's research, based on their

71. Pahnke et al., "The Experimental Use of Psychedelic (LSD) Psychotherapy," 56. Patients' drug reactions were classed as "profound," "marked," or "minimal" with the numbers of "essentially rehabilitated" in each of these categories tabulated. For global adjustment, percentage scores for these categories were 61, 39, and 24, respectively, and for drinking behavior were 61, 48, and 36.

72. Ibid., 57.

73. Kurland et al., "LSD in the Treatment of Alcoholics," 91–92.

deviation from the theory and method of psychedelic therapy. Instead of displaying the scientific method as an "impartial arbiter," Savage saw the Mendota researchers' clinical trial as representing "bias in, bias out": "What makes the work unscientific is that they make not the slightest effort to replicate the works that they are attacking except by employing the same name, psychedelic. . . . The point is not whether or not the psychedelic hypothesis is correct, but that they made no effort to test it."[74] In their review of previous study, Ludwig, Levine, and Stark had shown a firm understanding of the theory and method of psychedelic therapy, describing its goal of producing a transcendental experience through intensive patient preparation and the use of visual and auditory stimuli, which could promote positive changes in the patient in a similar manner to a conversion experience.[75] Yet their form of psychedelic therapy employed minimal preparation, a brief, conventional, insight-oriented psychotherapy session, little regard to "set and setting" and an antimystical focus. Hypnodelic therapy used hypnosis to improve control over the LSD session, but did not fundamentally alter the treatment. In essence, both treatments involved a single session of psycholytic therapy. However, that form of therapy usually involved numerous LSD sessions over an extended period of time, and as Savage stated, "I know of no one who has ever claimed that a single psycholytic session was curative of anything, least of all alcoholism." It is questionable whether Ludwig, Levine, and Stark could have themselves expected their treatment to be successful, as they recognized that with alcoholism, "All forms of insight orientated therapies . . . have been employed with equivocal or inconclusive results being obtained at best."[76] Despite their clear understanding of psychedelic therapy, and their treatment's striking dissimilarity to it, they continued to use the name "primarily for convenience."[77] This led Savage to accuse the researchers of designing an intentionally deceptive clinical trial: "It is apparent that they rejected the psychedelic model on moral grounds while pretending to test it."[78]

74. Charles Savage, "A Review of LSD and Alcoholism by Ludwig, Levine and Stark," 1970, unpublished manuscript, Folder 25, Charles Savage Addition 2, MSP 70, Charles Savage Papers, Archives and Special Collections, Purdue University Libraries, West Lafayette, Indiana, 7.
75. Ludwig et al., *LSD and Alcoholism*, 16.
76. Ibid., 4.
77. Ibid., 29, 88.
78. Savage, "A Review of LSD and Alcoholism," 1–8.

In response to these kinds of critiques, Ludwig, Levine, and Stark argued that although only 8.4 percent of their patients had a mystical experience, their data showed that there was no significant correlation between the "peak" response and therapeutic outcome. They also defended their minimal patient preparation on the basis that "virtually all patients seemed sufficiently prepared so as to experience the panoramic, spectacular effects of this drug without marked adverse reactions," and on the positiveness of patients' accounts of their experiences.[79] Savage pointed out the false logic in this assertion, comparing it to "justifying surgery on the basis that the patients did not bleed to death."[80]

Despite the Spring Grove researchers' attempt to design an adequately controlled clinical trial that appreciated the unique theory and method of psychedelic therapy, their evaluative method was questioned: Ludwig and his team criticized their lack of a nondrug control and possible nontherapy drug control. During the course of the Spring Grove trial, Levine had frequently visited the researchers as Chief of the Psychopharmacology Research Branch of the National Institute of Mental Health, and in retrospect, Savage wondered, "why he permitted some of the now obvious defects to remain uncorrected, unless he wished to give us plenty of rope."[81] In retrospect, the Spring Grove researchers conceded that a nondrug control would have been useful.[82] However, including a non-therapy drug control was a more complex issue. As Rick Doblin has argued, if Kurland and colleagues believed that their patient preparation and extensive psychotherapy was necessary to ensure safety and efficacy when administering LSD, giving the drug without these measures would be unethical.[83]

Ludwig, Levine, and Stark were also dismissive of the Spring Grove results, stating that "At the six-month evaluation, high-dose patients did not show significantly different amounts of drinking than low-dose patients when differences in other prognostic factors such as marital status were taken into account."[84] This opinion, apparently based on "currently reported results and informal communications," seems

79. Ludwig et al., *LSD and Alcoholism*, 241.
80. Savage, "A Review of LSD and Alcoholism," 7.
81. Charles Savage, "Looking Backwards through a Glass Darkly," undated, unpublished manuscript, Folder 33, Charles Savage Addition 2, MSP 70, Charles Savage Papers, 10.
82. Kurland et al., "LSD in the Treatment of Alcoholics," 92.
83. Richard Elliot Doblin, "Regulation of the Medical Use of Psychedelics and Marijuana" (PhD diss., Harvard University, 2000), 244.
84. Ludwig et al., *LSD and Alcoholism*, 236–37.

very unfair, if not misleading.[85] In their final 1971 report, Kurland and colleagues wrote that randomization had failed to control some important variables, with significant advantages to the high-dose group on marital status, high school completion, and numbers of hospital admissions for alcoholism. However, the groups were matched on "IQ, age, occupational status, and most importantly, on the pretreatment rating of abstinence."[86] In their evaluation of results, they suggested that the differences in the populations, as well as other variables, could have given the high-dose group an advantage, but that the great successes of both groups suggested otherwise.[87] Therefore, although they took the idea into account, the Spring Grove researchers did not decide that the uneven variables, such as marital status, accounted for the significant difference in drinking behavior at six months. Nor did they have the data needed to thoroughly assess this proposition.

Despite the significant flaws in Ludwig, Levine, and Stark's therapeutic method, the wider psychiatric community judged the trial on the scientific rigor of its design. In 1970, the study was granted the Hofheimer Award, from the American Psychiatric Association, for "developing a technique for administering a complex but precisely defined schedule for LSD treatment of chronic alcoholic patients, a method for studying it under controlled conditions, and for evaluating the clinical outcome in both qualitative and quantitative terms."[88] For psychiatrists who were not sensitive to the unique theories of psychedelic therapy, Ludwig's method would have indeed seemed watertight, and the inadequacies in therapeutic method would have gone unnoticed. In addition, in a discipline that was striving to solidify its scientific basis, a critique based on a lack of mystical focus would have seemed absurd. Ludwig's report would have been especially influential on the FDA who had a skeptical view of LSD's use in medicine, especially due to the lack of scientific rigor in previous studies. The study would have satisfied the agencies concerns for "adequate and well-controlled" studies and offered a firm conclusion, rare in previous reports, which affirmed their negative opinion. Although the Spring Grove research was also performed on a large scale and was adequately controlled, it

85. Ibid., 236.
86. Kurland et al., "LSD in the Treatment of Alcoholics," 85.
87. Ibid., 85.
88. Ludwig et al., *LSD and Alcoholism*, dust jacket.

could more easily be ignored as it continued the tradition of positive yet inconclusive results, and its scientific design was less impressive in conventional terms. Ultimately, in 1974, the National Institute of Mental Health reported that LSD had no therapeutic applications.[89]

CONCLUSION

In the 1950s, psychiatry's treatment landscape encompassed a complex mix of psychological, physical, and pharmaceutical methods. This is perhaps nowhere better demonstrated than in the example of LSD psychotherapy, where drug effects and psychotherapy were woven together to create a therapeutic experience greater than the sum of its parts. However, the Drug Amendments of 1962 separated psychiatry's pharmaceutical and psychological arms by requiring drugs to conform to efficacy standards that psychotherapies did not. This separation was widened as the amendments solidified the randomized double-blind controlled trial's status as the gold standard in efficacy testing; a method that was ill-suited to evaluate psychotherapies, and which carried with it the assumption that a drug's therapeutic activity was based on a direct biological action. This situation frustrated the progress of LSD psychotherapy research as psychiatrists struggled to design a trial that balanced scientific standards with LSD's unique therapeutic pathway. Disagreement over research design and controls moved research sideways instead of forward. A cyclic pattern emerged in which each research team set out with a critique of the trial design and therapeutic methods of previous researchers, attempted to right the wrongs, and were subsequently critiqued on the same bases by the next researchers.

For many LSD researchers, the desire to conform to the new standards of efficacy evaluation led them to ignore the therapeutic methods that had been central to the original claims of efficacy, leaving them with negative results. Charles Savage encapsulated this situation in the conclusion of his critique of Ludwig's study, stating, "LSD seems to be a facilitator and in the present study it seems to have facilitated mediocrity, however brilliantly reported and adumbrated by elegant statistical techniques."[90] However, with faith in scientific rigor so high, many psychiatrists saw the failure of LSD to perform under

89. Sidney Cohen and Stanley Krippner, "Editors' Introduction," *J. Psychoactive Drugs*, 1985, *17*, 213–17, 216.
90. Savage, "A Review of LSD and Alcoholism," 8.

scrutiny as proof of its uselessness, regardless of the inhospitable evaluative conditions.

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