

CHAPTER 4
REGULATORY, ETHICAL AND METHODOLOGICAL ISSUES
IN PSYCHEDELIC RESEARCH

Congress has expressly given the FDA the regulatory authority to review for possible approval all proposed clinical trials investigating the potential risks and benefits associated with the medical uses of psychedelics and marijuana.⁸⁹⁸ FDA also has been given the responsibility to evaluate all the data gathered in these clinical trials to determine if applications for the prescription use of these drugs should be approved.⁸⁹⁹ As Chapters 1-3 have demonstrated, the issue of whether such research should take place at all has recently been answered in the affirmative by the FDA as well as by several corresponding regulatory agencies around the world. As research is gradually conducted, the task of evaluating the data generated will be complicated by challenging methodological issues and passionately divisive political controversy. In order to protect and promote the health and safety of research subjects, patients, and the general public, a variety of difficult regulatory, ethical and methodological issues need to be examined carefully. Chapters 4-5 are a contribution toward that effort.

In order to focus the analysis, Chapters 4-5 concentrate on a thorough review of issues related to the design of psychedelic psychotherapy research protocols and the standards of proof utilized to evaluate that research. Medical marijuana research is discussed but not systematically evaluated, although many of the issues covered in Chapters 4-5 are relevant to the regulatory review of the medical uses of marijuana. In discussing the medical uses of psychedelics, the term “psychedelic psychotherapy” will be used to mean the combination of a specific psychedelic drug administered within a specific psychotherapeutic context. Research with one form of psychedelic psychotherapy will not be assumed to generalize to other forms.

The analysis of regulatory, ethical and methodological issues conducted in Chapter 4 results in the conclusion that essentially the same standard of proof and associated protocol designs that FDA uses to review other drugs for possible prescription use are sufficiently rigorous for the review of the possible prescription use of psychedelics and marijuana. This conclusion is similar to the 1992 recommendation of FDA’s Drug Abuse Advisory Committee, which led to the establishment of FDA’s currently-held policy regarding criteria for the review of research protocols with psychedelic drugs and marijuana.

In Chapter 5, political factors that may necessitate more complex protocol designs and a higher standard of proof are taken into account. Chapter 5 includes a critical evaluation of all currently-approved psychedelic psychotherapy research protocols and proposes an

⁸⁹⁸Kefauver-Harris Amendments of 1962 to the 1938 Food, Drug, and Cosmetic Act. 87 P.L. 781; 76 Stat. 780. October 10, 1962; also Federal Food, Drug, and Cosmetic Act of 1938. 75 P.L. 717; 75 Cong. Ch. 675; 52 Stat. 1040. June 25, 1938.

⁸⁹⁹Ibid.

enhanced design for any large-scale trials of the safety and efficacy of psychedelic psychotherapy. The economic implications of this enhanced design are evaluated and determined not to impose an unreasonable burden on sponsors of research into potential medical uses of psychedelics or marijuana.

Regulatory and Ethical Issues: The Standard of Proof

One of the major regulatory policy issues associated with psychedelic psychotherapy research concerns what standard of proof should be used for decisions related to the potential approval of a psychedelic drug for prescription use. The usual standard of proof used by FDA is whether a drug has been shown to be more effective than an inactive placebo in treating symptoms or curing a disease. The issue with psychedelic psychotherapy research is whether psychedelic drugs, all of which have been classified by the Controlled Substances Act as having a “high potential for abuse,”⁹⁰⁰ should be held to a higher standard as a result of their abuse potential.

One standard would be to insist that a psychedelic drug be approved only if comparative studies testing it against a drug already approved for the same clinical indication show it to be equivalent in efficacy to the already approved drug. An even higher standard would be to require that psychedelic psychotherapy be proven equivalent not just to any approved drug for the same clinical indication, but to what is generally considered to be the most effective approved drug for that condition, if there is such a clear leader among the relevant approved drugs. The highest standard would be to require psychedelic psychotherapy to be superior to all currently available treatments. Policies regarding standards of proof will have a direct impact on the question of protocol design for efficacy studies.

The determination of the appropriate standard of proof for psychedelic psychotherapy also has several ethical dimensions. These are of general applicability and also apply to psychedelic psychotherapy research design and evaluation. The use of a standard of proof comparing psychedelic psychotherapy against placebos may give patients and their physicians a larger choice of approved medications than would the use of higher standards of proof. Narrowing choice through the use of higher standards will restrict treatment options and negatively impact some subsets of patients. Another issue that cuts the other way is that it may be unethical in certain circumstances to randomize patients to placebo control groups, especially when approved treatments already exist for the clinical indication being studied, even if the treatments are of marginal efficacy.^{901 902} If and when

⁹⁰⁰ Sec. 202 (b) (1) (A), Controlled Substances Act of 1970. 91 P.L. 513; 84 Stat. 1236. October 27, 1970.

⁹⁰¹ Rothman K, Michels K. The continuing unethical use of placebo controls. *N Engl J Med* 331 (Aug 11, 1994) 6:394-8.

⁹⁰² Lieberman J, Stroup S, Laska E, Volavka J, Gelenberg A, Rush J, Shear K, Carpenter W. Chapter 2-

the use of placebo control groups in psychedelic psychotherapy research protocols is determined to be unethical, different protocol designs will be needed and a different standard of proof will be required.

Methodological Issues in Protocol Design

Evaluating the safety and efficacy of psychedelic psychotherapy research raises a variety of methodological issues. The primary methodological difficulty stems from the subjective effects of psychedelics, which provide both subjects and experimenters ample opportunity to guess accurately at a rate much better than chance whether subjects received either the test drug or a placebo. These subjective clues compromise the ability of the researchers to conduct an effective single-blind study, in which the subjects are unaware of whether they received the test drug or placebo, or double-blind study, in which both the subjects and the experimenters are unaware of whether test drug or placebo was administered. The difficulties in conducting a double-blind study with psychedelics create a vexing methodological issue complicating the choice of appropriate control groups for psychedelic psychotherapy efficacy studies.

This chapter includes a discussion of the history and purpose of the double-blind research design. The weaknesses in the implementation of the double-blind methodology even in conventional psychiatric research with standard pharmacological agents for the treatment of psychiatric indications is reviewed. The difficulties in conducting a successful double-blind study of psychedelic psychotherapy are highlighted through a review of past research and an evaluation of the informed consent forms of all currently approved studies designed to investigate the therapeutic potential of psychedelics. Counterproductive aspects of the double-blind method when applied to psychedelic psychotherapy are discussed, as are claims that there has been an overreliance on the double-blind method in drug development. Alternatives to double-blind methodology are proposed.

Another challenging methodological issue involves the need to evaluate the contribution of both pharmacological and non-pharmacological psychotherapeutic process components involved in psychedelic psychotherapy. FDA has no regulatory authority over the practice of psychotherapy and thus may have little or no experience reviewing and evaluating psychotherapeutic techniques. With psychedelic psychotherapy, the therapeutic approach within which the psychedelic drug is administered is an important variable that may have a substantial impact on therapeutic outcome.⁹⁰³ As a result, the non-pharmacological psychotherapeutic technique must be scientifically standardized and its impact evaluated to the extent possible. The dual nature of the treatment involving both the

Issues in Clinical Research Design: Principles, Practices, and Controversies. in (ed.) Pincus H, Lieberman J, Ferris S. *Ethics in Psychiatric Research- A Resource Manual for Human Subjects Protection*. Washington, DC: American Psychiatric Association, 1999: 23-60.

⁹⁰³Grof S. *LSD Psychotherapy*. New York: Hunter House, 1980. see also Naranjo C. *The Healing Journey- New Approaches to Consciousness*. New York: Pantheon-Random House, 1973.

psychedelic drug itself and an associated therapeutic approach suggests the benefits of a renewed collaboration in the review of psychedelic research protocols between FDA and the National Institute of Mental Health (NIMH), which has previously supported research into the comparative effectiveness of several different forms of psychotherapy and pharmacotherapy in the treatment of depression.⁹⁰⁴

Standard of Proof For Determining Efficacy

The FDA generally requires evidence of efficacy from at least two “adequate and well-controlled clinical investigations” in which the test drug is compared to any of a variety of control conditions, with the minimum requirements involving an inactive placebo control.⁹⁰⁵ Congress has left it to the FDA to determine just how an adequate and well-controlled trial is to be designed.⁹⁰⁶ In practice, the FDA most frequently bases its decision whether or not to approve a drug for marketing on data about a drug’s safety and efficacy that have been gathered through the use of randomized, double-blind, placebo-controlled studies.⁹⁰⁷ As one regulatory official has stated, “For many years, the gold standard for demonstrating the efficacy of new therapeutic agents has been the double-blind, placebo-controlled clinical trial.”⁹⁰⁸

The “adequate and well-controlled clinical investigations” required by FDA generally do not need to demonstrate that the new drug is as effective as or more effective than other drugs already on the market. The standard for approval is usually measured against the disease, not against alternative treatments, with the drug needing simply to be more effective than a placebo.⁹⁰⁹ FDA regulations state, “the test drug is compared with an inactive preparation designed to resemble the test drug as far as possible. A placebo-controlled study may [but need not] include additional treatment groups such as an active treatment control or a dose comparison control.”⁹¹⁰ Dr. D.J. Lyons, Irish Medicines Board, commented on the

⁹⁰⁴Elkin I, Parloff M, Hadley S and Autry J. NIMH Treatment of Depression Collaborative Research Program. Background and research plan. *Arch Gen Psychiat*42 (Mar 1985) 3:305-16.

⁹⁰⁵See 21 CFR 314.126. Adequate and well-controlled studies. Part 314 --Applications for FDA Approval to Market a New Drug, Subpart D- FDA Action on Applications and Abbreviated Applications.

⁹⁰⁶See also Campbell D, Stanley J. *Experimental and Quasi-Experimental Designs for Research*. Boston: Houghton Mifflin, 1963; and Regelman R, Hirsch R. *Studying a Study and Testing a Test: How to Read the Medical Literature. Second Edition* Boston: Little, Brown and Co., 1989.

⁹⁰⁷FDA has approved drugs for marketing based entirely on data gathered from published literature. FDA Guidance for Industry. Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products:19.

⁹⁰⁸Lyons D. The Use and Abuse of Placebo in Clinical Trials. *Drug Info J* 33 (1999) 1: 261.

⁹⁰⁹Wardell W, Lasagna L. *Regulation and Drug Development*. Washington, DC. American Enterprise Institute for Public Policy Research, 1975:40.

⁹¹⁰21 CFR 314.126 (b) (2) (i).

differences between US and European standards, noting, “The Food and Drug Administration is commonly understood to require demonstrations of efficacy in placebo-controlled trials in circumstances where ethically possible, and has traditionally laid greater emphasis on requiring placebo-controlled studies than has been the case in Europe.”⁹¹¹

In certain limited circumstances, when a drug makes a direct and relatively immediate contribution to preventing mortality or irreversible morbidity, FDA can insist that a new drug be approved only if there is evidence of equivalent efficacy to standard medications.^{912 913} Though comparative trials are rarely needed to obtain approval for marketing, physicians and health insurance organizations may need to see the results of comparative trials before being willing to replace medications they already use with a newly approved medication. ⁹¹⁴ Comparative trials are more common in Europe than in the US, in part because the many national health care systems throughout Europe want comparative data to aid in pharmacoeconomic decisionmaking concerning which drugs to purchase.

Data from two independent trials, rather than just one, are generally required as the basis for FDA approval. All clinical trials are subject to bias, so requiring two independent trials rather than just one reduces “the chances that a biased, chance, site-specific or fraudulent result will lead to an erroneous conclusion that a drug is effective.”^{915 916}

⁹¹¹Lyons D: 264.

⁹¹²personal communication, Dr. Murray Lumpkin, Deputy Center (CDER) Director for Review Management, February 18, 2000.

⁹¹³Comparative trials in humans assessing bioequivalence may be required to compare generic drugs to the drugs for which they are meant to substitute. New clinical trials are not required to compare equivalence in the underlying data supporting safety and efficacy. Organization of an ANDA (Abbreviated New Drug Application). FDA Guidance to Industry. February 1999. <http://www.fda.gov/cder/guidance/index.htm>

⁹¹⁴ICH Draft Consensus Guideline, Choice of Control Group in Clinical Trials, Released for Consultation at Step 2 of the ICH process on May 7, 1999. Section 2.1.7.4 No Comparative Information, states, “placebo-controlled trials lacking an active control give little useful information about comparative effectiveness, information that is of interest in many circumstances. Such information cannot reliably be obtained from cross-study comparisons, as the conditions of the studies may have been quite different.

⁹¹⁵Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products. FDA Guidance to Industry. May 1998: 5. <http://www.fda.gov/cder/guidance/1397fnl.pdf>

⁹¹⁶Several interesting new approaches for the conduct of Phase 3 trials have recently been proposed. Josef Hogel, Ph.D. and Wilhelm Gaus, Ph.D., University of Ulm, Germany, have proposed that the perceived need of a regulatory agency to verify the results presented to it by self-interested pharmaceutical companies leads to “excessive documentation and to costly monitoring and auditing costs, which are intended to ensure the credibility of the results.” They cite K.R. Popper and propose that a more socially efficient process would require the initial Phase 3 trials to be conducted by the pharmaceutical companies, with “confirmatory trials [conducted] independent of the sponsor and supervised by the regulatory bodies.” They do, however, note that whether, “the increase in the power and responsibility of the regulatory bodies that

However, the FDA Modernization Act of 1997 does give FDA the authority to approve a drug if the proof of its effectiveness is based on a minimum of one “adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation).”⁹¹⁷ The instances where one large-scale trial may be considered sufficient are usually those in which the study was rigorously well-controlled so that “the possibility of bias due to baseline imbalance, unblinding, post-hoc changes in analysis, or other factors is judged to be minimal.”⁹¹⁸ Such studies are usually conducted in a patient population suffering from a serious condition for which there were no or only minimally effective and/or safe alternative medications, where the “trial demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with a potentially serious outcome,”⁹¹⁹ with beneficial outcomes that “reflect a clear prior hypothesis documented in the protocol.”⁹²⁰ Furthermore, replication of such a study would usually present ethical problems associated with the randomization of some patients to a placebo control group after the initial trial had already developed substantial evidence supporting the efficacy of the new drug. However, “a single favorable study among several similar attempts that failed to support a finding of effectiveness would not constitute persuasive support.”⁹²¹

Does High Abuse Potential Require Higher Standards of Proof?

would be involved would be of benefit or otherwise is a question that can only be speculatively answered at the moment.” Hogel J, Gaus G. The Procedure of New Drug Application and the Philosophy of Critical Rationalism or The Limits of Quality Assurance with Good Clinical Practice. *Contr Clin Trial* 20 (1999): 513-519. An alternative proposal suggesting instead the enrolling of more patients in confirmatory trials is offered in Darbyshire J. Confirmatory Trials- A New Approach? *Contr Clin Trial* 20 (1999): 567-568. Yet another proposal by Drs. Palmer and Rosenberger discusses the potential benefits and ethical advantages that can be derived from the constant analysis of data as soon as it is generated, rather than waiting either for certain milestones to be reached or the trial to be completed, along with the application of sequential stopping rules, Bayesian, and adaptive designs. The purpose of such constant monitoring is to determine at the earliest moment if and when the data that are being generated permit reliable conclusions to be drawn about the outcome of the study, without the need to complete the study. Drs. Palmer and Rosenberger note, “In realization of the ethical shortcomings of totally ignoring the accruing data, conventional trials have adopted data and safety monitoring boards to interrupt an ongoing trial if they judge it ethically appropriate to do so.” Palmer C, Rosenberger W. Ethics and Practice: Alternative Designs for Phase III Randomized Clinical Trials. *Contr Clin Trial* 20 (1999): 172-186.

⁹¹⁷Sec 115 (a) Clinical Investigations. FDA Modernization Act of 1997.

⁹¹⁸Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products: 6.

⁹¹⁹Ibid., 13.

⁹²⁰Ibid., 6.

⁹²¹Ibid., 6.

In 1992, the Pilot Drug's Drug Abuse Advisory Committee evaluated the question of whether the review of IND applications to study Schedule I drugs should be judged on a different standard than other IND applications. Near the end of the open session, Dr. Curtis Wright, Medical Review Officer, Pilot Drug, stated "I have not heard anything that leads me to believe that this is a qualitatively different kind of research than the rest of research that we do with other agents, especially agents that act on the brain." The Acting Chair of the Advisory Committee, Dr. Richard Meisch, concurred, "Speaking for myself, I agree with your assessment."⁹²² The other members of the Advisory Committee agreed that the risks of psychedelic drugs, *when used within an FDA-approved and IRB-approved clinical research setting*, were not necessarily greater than the risks of other drugs reviewed by FDA. The outcome of the meeting was that the Advisory Committee voted to recommend that the normally rigorous standards applied by FDA to the review of research with other drugs be considered sufficient for the regulation of research with psychedelic drugs. FDA's Pilot Drug staff accepted the recommendation and began immediately acting upon it, approving that afternoon in the closed session a Phase I dose-response study of MDMA to be conducted by Dr. Charles Grob at UC Irvine.⁹²³

In the eight years since the recommendation of the Advisory Committee was adopted by FDA, nothing in the subsequent conduct of research with Schedule I drugs has called that decision into question.⁹²⁴ Furthermore, FDA's policy as it related to medical marijuana research was reaffirmed in 1994 by the Director of the Office of National Drug Control Policy,⁹²⁵ and its policy in relation to both medical marijuana and psychedelic research was reaffirmed in 1999 by Dr. Janet Woodcock, CDER Director.⁹²⁶

If the policy established for the regulation of research with psychedelic drugs were to be extended to the possible future review of NDAs for the prescription use of psychedelics, the same standards that apply to the approval of other drugs would be considered sufficient for the approval of psychedelics. Whether or not the same standards should apply turns in large part on whether the medical use of psychedelics *as controlled prescription medications* can be effectively regulated to minimize misuse, abuse and diversion.⁹²⁷ If the abuse potential of psychedelics as prescription medicines can be

⁹²²Transcript of the Drug Abuse Advisory Committee, 23rd Meeting, Volume 11, Open Meeting, July 15, 1992: 78.

⁹²³Grob C, Poland R, Chang L, Ernst T. Psychobiologic effects of 3,4-methylenedioxymethamphetamine in humans: methodological considerations and preliminary observations. *Behav Brain Res* 73 (1996) 1-2:103-7.

⁹²⁴personal communication, Dr. Wright, March 8, 1999; personal communication, Dr. Janet Woodcock, June 8, 1999.

⁹²⁵Brown L. Director, Office of National Drug Control Policy. Letter to DEA Administrator Tom Constantine. July 5, 1994.

⁹²⁶personal communication, Dr. Janet Woodcock, June 8, 1999.

substantially controlled, either by some or all of the current set of regulations governing the prescription use of other Schedule II drugs or by regulatory mechanisms FDA has used for other medications, then the application of the same standards of proof used for the approval of other drugs may be appropriate for the approval of psychedelics as medicines.

To evaluate whether the high abuse potential of psychedelics *as controlled prescription medications* is fundamentally different than the abuse potential of all other Schedule II medications, it is essential to take into account that the medical use of psychedelics would be as an adjunct to psychotherapy. Psychedelic medicines are intended to be administered under the direct supervision of a physician or therapist. They will not be prescribed as take-home drugs to be self-administered on a daily or any other basis. This dramatically reduces the abuse potential of these substances as prescription medications (and also reduces the risks to patients in clinical trials).⁹²⁸ Diversion by patients will be virtually a non-issue, since patients would be required to consume the medications that are prescribed for them while they are under the direct supervision of their therapist.⁹²⁹ Diversion by

⁹²⁷Joranson D. Guiding Principles of International and Federal Laws Pertaining to Medical Use and Diversion of Controlled Substances. in (eds.) Cooper J, Czechowicz D, Molinari S. *Impact of Prescription Drug Diversion Control Systems on Medical Practice and Patient Care*. NIDA Research Monograph Series #131. Washington, DC, NIH Publication #93-3507. 1992: 18-34.

⁹²⁸Some fraction of patients who are first exposed to psychedelics in the context of medical treatment might subsequently be motivated to purchase these drugs on the black market for non-medical purposes. This has not, however, been reported as a problem associated with the psychedelic psychotherapy research conducted in the 1950s and 1960s. One factor limiting this possibility is that psychedelic psychotherapy involves the confrontation, acceptance and integration of challenging emotions and insights, reducing the association of psychedelics with “fun.” Similarly, the use of synthetic narcotic painkillers in childbirth does not seem to have generated a subsequent demand for the use of these drugs non-medically. In a study of 11,882 patients who received morphine for control of pain related to cancer, only 4 subsequently became addicted (Chapman C, Hill C. Prolonged morphine self-administration and addiction liability. *Cancer* 63 (1989):1636-1644.) If some psychedelic psychotherapy patients do seek out black market supplies, their prior medical use of psychedelics in a context of trained therapists working in a safe, protected environment will at least have demonstrated the value of carefully choosing the set and setting. The converse phenomenon is also possible, since in the absence of a legal context for psychedelic psychotherapy some people may seek out psychedelics from the black market for purposes of self-medication, taking these drugs in riskier settings. While difficult to estimate, the harmful consequences resulting from patients seeking out black market supplies of psychedelics for non-medical uses after receiving professional care are not likely to be large.

⁹²⁹It is possible to divert drugs that are administered for immediate consumption, as happens sometimes with single doses of methadone. The diversion of psychedelics, where patients would be expected to remain for hours after dosing, would be much more difficult than the diversion of methadone, where patients go to the clinic to pick up their dose and then depart. Inciardi J. *Methadone Diversion: Experiences and Issues*. NIDA Services Research Monograph Series. Washington, DC, U.S. Government Printing Office, 1977.

manufacturers and distributors can be substantially eliminated in the same manner as diversion of all other Schedule II drugs is controlled, through the close monitoring of inventories.⁹³⁰ Diversion by pharmacists and physicians can also be controlled through existing methods,⁹³¹ as well as through the use of a system to be proposed in Chapter 6 for distribution only through the mail with records kept of each patient treated.

More important than the issue of diversion is whether the misuse of these drugs by physicians can be controlled so that physicians can in actual practice safely administer these drugs to their patients. While the FDA will not approve these drugs unless they have been safely and effectively administered to patients in the context of Phase III clinical trials, the prescription use of medicines generally ends up being much less controlled than the use of the same medications in the context of clinical trials. For psychedelic psychotherapy, a series of regulatory mechanisms can be put into place that will substantially enhance the likelihood that the physicians who prescribe these drugs will do so with a high degree of safety and circumspection. How these regulatory mechanisms will be designed, implemented and enforced will be the topic of Chapter 6. They will be mentioned here only in passing. They include educational and training requirements for all physicians interested in prescribing these drugs to their patients, limited distribution by mail through one central pharmacy to ensure that only physicians with special licenses can prescribe these drugs, minimum standards for the physical facilities in which these drugs can be prescribed,⁹³² minimum staffing requirements for these facilities, required educational programs for all staff with direct patient contact, limitations on advertising, and a national registry of patients who receive psychedelics so that follow-up outcome studies can be conducted into the long-term effects of the treatments.

Whether a convincing case can be made that these measures are practical, effective, and feasible to implement is addressed in Chapter 6. Assuming that such a case can be made, it is likely that the abuse potential of psychedelics *as prescription medicines* would be no greater, and perhaps less than, other Schedule II drugs. Therefore, the abuse potential

⁹³⁰ The DEA's Automation of Reports and Consolidated Order Systems (ARCOS) track the manufacture and distribution of controlled substances intended for medical uses. According to G. Thomas Gitchel, Chief, Liaison and Policy Section, Office of Diversion Control, DEA, "tight access and accountability controls at the wholesale level have all but eliminated diversion at that level." Gitchel G. Existing Methods to Identify Retail Drug Diversion. in (eds.) Cooper J, Czechowicz D, Molinari S. *Impact of Prescription Drug Diversion Control Systems on Medical Practice and Patient Care*. Washington, DC: NIDA Research Monograph Series #131. Washington, DC, NIH Publication #93-3507. 1992:134.

⁹³¹ Horgan C, Prottas J, Tompkins C, Wastila L, Bowden M. Summary and Conclusions of a Review of Prescription Drug Diversion Control Methods. in (eds.) Cooper J, Czechowicz D, Molinari S. *Impact of Prescription Drug Diversion Control Systems on Medical Practice and Patient Care*. Washington, DC: NIDA Research Monograph Series #131. Washington, DC, NIH Publication #93-3507. 1992: 206-223.

⁹³² Examples of drugs administered only on an in-patient basis are some cancer chemotherapy drugs, cocaine, ketamine and other anesthetics.

of psychedelics would not justify the imposition of a higher standard of proof than the comparison against placebo that FDA currently applies with other drugs.

Does Impact of Approval on Non-Medical Use Justify Higher Standards?

In addition to the direct abuse potential of psychedelics as prescription medicines, the impact of the approval of psychedelic psychotherapy on the non-medical use of psychedelic drugs and on drug abuse prevention efforts must be considered. The theory of such indirect effects, sometimes referred to as “sending the wrong message,” is that accepting the medical use of Schedule II drugs such as psychedelics and marijuana will reduce the perceived risk of these drugs, thereby increasing the willingness of young people and others to use these drugs in a non-medical context. While it is true that there is a negative correlation between “perceived risk” of Schedule I drugs and the amount of adolescent drug use,⁹³³ the case of medical marijuana is instructive here. There is no evidence demonstrating that public support for the medical use of marijuana has impacted the way adolescents or adults perceive its risk, or has increased non-medical use.

The medical use of marijuana has received increasingly favorable media attention since the first medical marijuana state initiatives passed in California and Arizona in November 1996. Nevertheless, a survey conducted from 1997-1998 and funded by the State of California determined that the use of marijuana by teenagers has remained essentially constant since the passage of the medical marijuana initiative. The survey found that 41.6 percent of California’s eleventh graders had used marijuana in the 1997-98 period, compared to 42.8 percent in 1995-96. In contrast, in the Eastern part of the country where there were no medical marijuana initiatives, the survey reported that there was an increase in marijuana usage among twelfth graders, from 40 percent in 1995-96 to 43.5 percent in 1997-98.⁹³⁴

⁹³³Bachman J, Johnston L, O'Malley P. Explaining the recent increases in students' marijuana use: The impact of perceived risks and disapproval from 1976 through 1996. *Amer J Pub Health* 88 (1998): 887-892.

⁹³⁴7th Biennial Cal. Student Substance Use Survey: Grades 7, 9, and 11, 1997-8: Preliminary Findings" Nov. 1998; Rodney Skager and Gregory Austin, Project Directors; Sponsored by Cal. Dept of Justice, Office of the A.G., Crime and Violence Prevention Center; Cal. Dept of Education, Healthy Kids Program Office; Dept of Alcohol & Drug Programs; and Dept of Health Services, Office of AIDS. This report has not been officially released yet. On May 27, 2000, California NORML put out a press release claiming that the report was being suppressed for political reasons (<http://www.canorml.org/news/skagerstudy.html>) because the study failed to support one of the central arguments against California’s Proposition 215, that passage would “send the wrong message” to kids and increase non-medical marijuana use. Dr. Skager, professor emeritus of the UCLA Graduate School of Education and founding director of the California Attorney General’s Student Survey on drug use, was quoted in the press release saying that his findings have been “under review” by the DADP for the past two years, and that “I wonder if it will ever see the light of

The results of the California survey were confirmed by a federally-funded survey, the 1998 National Household Survey on Drug Abuse (NHSDA), which reported that. "In response to propositions passed by voters in California and Arizona in 1996 for the legalization of some illicit drugs for certain medical uses, the NHSDA sample was supplemented in those states in 1997 and 1998 to measure the potential impact of these voter initiatives."⁹³⁵ The report noted that samples sizes for California were large enough in 1995 and 1996 "to allow examination of longer term trends for that state."⁹³⁶ The results of these surveys failed to demonstrate any significant link between the substantial amounts of favorable publicity and public support for the medical use of marijuana and subsequent non-medical use patterns in those two states. In California, marijuana use at least once in the past month for all ages combined declined from 6.0% in 1996 to 5.9% in 1997 and 5.5% in 1998.⁹³⁷ The report noted that, "rates [of marijuana use] for both youths and adults have been stable since 1995."⁹³⁸ In Arizona, marijuana use for all age groups combined declined from 6.1% in 1997 to 5.1% in 1998.⁹³⁹ In addition, among Arizona youths aged 12-17, "there were significant increases in the percentage reporting great risk in using marijuana once or twice a week (from 46.6 percent to 52.7 percent)."⁹⁴⁰ Nationally "annual prevalence rates peaked in 1996 at 8th grade and in 1997 at 10th and 12th grade. Some decline followed but there was no further decline observed in 1999, specifically."⁹⁴¹

Of course, it cannot be determined whether these declines in use or increases in day? Almost two years have passed since delivery of the first draft. People in the sponsoring agency undoubtedly fear the consequences of release of the data. The findings are politically incorrect because federal propaganda about the medical marijuana initiative insisted that passage would 'send the wrong message to young people.'

⁹³⁵National Household Survey on Drug Abuse, 1998. II. California and Arizona. Office of Applied Studies, SAMHSA. Report Issued August 1999: 32. <http://www.samhsa.gov/NHSDA.htm>

⁹³⁶Ibid., 32.

⁹³⁷National Household Survey on Drug Abuse, 1998. Table 58. Percentages Reporting Past Month Use of Illicit Drugs, Alcohol and Tobacco for California, by Age Groups: 1995-1998. Office of Applied Studies, SAMHSA. Report Issued August 1999: 125. These differences were not statistically significant. <http://www.samhsa.gov/NHSDA.htm>

⁹³⁸Ibid., 32.

⁹³⁹National Household Survey on Drug Abuse, 1998. Table 60. Percentages Reporting Past Month Use of Illicit Drugs, Alcohol and Tobacco for Arizona, by Age Groups: 1997-1998. Office of Applied Studies, SAMHSA, Report Issued August 1999: 127. These differences were not statistically significant. <http://www.samhsa.gov/NHSDA.htm>

⁹⁴⁰Ibid., 33.

⁹⁴¹Johnston L, O'Malley P, Bachman J. The Monitoring the Future National Survey Results on Adolescent Drug Use- Overview of Key Findings, 1999. NIH Publication No. 00-4690, Washington, DC U.S. Government Printing Office, 2000: 8. <http://monitoringthefuture.org/pubs.html>

perceived risk would have been more substantial in the absence of the medical marijuana initiatives. Nevertheless, the data certainly suggest that the impact of positive information and public support for the medical use of marijuana will not overwhelm other sources of information or motivations for the use of marijuana.

In regard to the possible approval of MDMA-assisted psychotherapy or other forms of psychedelic psychotherapy as prescription medicines, Dr. Mark Kleiman comments, “On balance, it seems likely that the approval of MDMA for clinical use will tend to foster non-medical use as well, or at least speed the pace at which knowledge of the drug’s effects, and interest in experiencing them, spreads. But it also seems likely that non-medical use will be present whether or not clinical use is approved, and the eventual size of the illicit market may depend very little on the decision to approve or disapprove the use of MDMA in psychotherapy.”⁹⁴² At present, knowledge about the subjective effects of MDMA as well as the amount of its non-medical use is growing at a dramatic rate.^{943 944} ⁹⁴⁵ Dr. Leshner, NIDA Director, has commented, “We’re not yet at epidemic proportions, but we are seeing an increase of Ecstasy and other club drugs in every major city and among high school students. We’re trying to use science to get in the way of a potential public health plague.”^{946 947} Since the FDA has not yet approved any research into the therapeutic use of MDMA, much less approved the drug for use in psychotherapy, this rise in MDMA

⁹⁴²Kleiman M. Proposed Therapeutic Uses of MDMA: Risks and Benefits in Decisions about Research Approval and Approval as Medicine. *Conference on Clinical Research with MDMA and MDE*. Dead Sea, Israel. Sept 1, 1999. <http://www.maps.org/research/mdma/israel/kleimantalk.html>

⁹⁴³“In a 1999 survey, 8.0 % of high school seniors reported they had tried Ecstasy, up from 5.8% the previous year.” from article by Mertl M. Ecstasy and the Brain: Club Drug Rants and Raves. *Brain.Com*. April 11, 2000. http://www.brain.com/about/article.cfm?id=9300&cat_id=500

⁹⁴⁴ “U.S.A. Customs officials have seized almost 3.5 million pills in January and February of this year (2000) alone, more than 10 times the amount sold in all of 1993. “ from article by Mertl M. Ecstasy and the Brain: Club Drug Rants and Raves, April 11, 2000, http://www.brain.com/about/article.cfm?id=9300&cat_id=500

⁹⁴⁵The non-medical use of MDMA (Ecstasy) is increasing around the world and has been claimed to be reaching epidemic proportions. See 4/3/2000 CNN.com article, “Ecstasy seizures suggest drug’s flow becoming epidemic.” <http://robots.cnn.com/2000/US/04/03/designer.drug.deluge.ap/index.html>

⁹⁴⁶Leinwand D, Fields G. Party’s Over: Studies show drug causes brain damage. *USA Today* (April 19, 2000): A2.

⁹⁴⁷Data gathered upon direct request by Substance Abuse Mental Health Services Administration (SAMHSA), Office of Applied Studies, 3/31/2000, indicates that Medical Examiner data reports one death in 1994 associated with, but not necessarily causally linked to, MDMA, six in 1995, eight in 1996, three in 1997, nine in 1998. Hospital emergency room visits reported by the DAWN system as being associated with MDMA, but not necessarily causally linked to it, numbered 247 in 1994, 422 in 1995, 319 in 1996, 637 in 1997, 1142 in 1998.

use is clearly independent of any official approval of its therapeutic use. If and when MDMA-assisted psychotherapy is approved as a medicine, it will follow a substantial amount of public information disseminated by NIDA on the risks of MDMA. Given Dr. Leshner's rhetoric of epidemics and plague, NIDA's educational campaign is likely to be extensive⁹⁴⁸ and should ensure that if MDMA is ever approved as a medicine, information about that approval will be delivered to a public thoroughly inoculated against the use of MDMA.⁹⁴⁹

If the medical use of marijuana or psychedelic psychotherapy does become approved by the FDA, direct-to-consumer advertising could become a new source of public information about the medical uses of these drugs. The effect of direct-to-consumer advertising on non-medical use may have a stronger impact than other sources of information, since it would convey the full approval of all regulatory authorities. It is unclear whether this would have a greater impact on the public's use of psychedelics than the negligible effect on marijuana use that occurred when a majority of several states' voters approved medical marijuana initiatives. As will be suggested in Chapter 6, it may be wise to limit direct-to-consumer advertising in a voluntary agreement with any sponsors of psychedelic psychotherapy, at least initially.⁹⁵⁰ Even if direct-to-consumer advertising were allowed, under the procedures outlined in Chapter 6 only a small number of licensed practitioners and licensed facilities could initially deliver psychedelic psychotherapy. This would limit the economic benefits of direct-to-consumer advertising and the extent of such advertising. If direct-to-consumer advertising were permitted, neither the target audience nor the entire spillover audience for these messages would be large. Any impact that direct-to-consumer advertisements had on increasing the non-medical use of psychedelics would likely be minimal. Studies of the local impact of such advertising could be conducted before

⁹⁴⁸NIDA News Release, December 2, 1999. "Club Drugs Take Center Stage in New National Education and Prevention Initiative by NIDA and National Partners- Initiative Includes Research Funding and Community Outreach." <http://165.112.78.61/MedAdv/99/NR-122.html> "As part of a national initiative to combat the increasing use of club drugs, the National Institute on Drug Abuse (NIDA) today announced that it will raise its funding for research about club drugs and what to do about them by 40 percent, bringing the total committed to this important effort to \$54 million. In addition, NIDA and four national organizations [the American Academy of Child and Adolescent Psychiatry (AACAP), the Community Anti-Drug Coalitions of America (CADCA), Join Together, and National Families in Action (NFIA)] launched a multi-media public education strategy to alert teens, young adults, parents, educators and others about the dangers of club drugs such as Ecstasy, GHB and Rohypnol, which are often used at all night "raves" or dance parties and have potentially life-threatening effects.

⁹⁴⁹There are always new generations to educate. However, with drug abuse prevention educational programs such as DARE reaching 5th graders, it is unlikely that more than a few people will have their first exposure to information about MDMA be about its approved medical use.

⁹⁵⁰Mr. Hutt has pointed out that it is highly doubtful that sponsors would use direct-to-consumer ads because of the potential for product liability suits.

such advertising became more widespread. It is also conceivable that increased public awareness about the medical use of psychedelics could reduce the risks of the casual non-medical use of psychedelics by spreading awareness of the enhanced safety associated with the administration of psychedelics within safe, supportive environments under the supervision of trained personnel. As Dr. John Halpern has speculated, “Research that identifies key factors for minimizing health risks or maximizing possible benefits may reduce dangerous drug use by teaching parameters needed for reasonable safety.”⁹⁵¹ Information about the treatment model for the therapeutic use of psychedelics could influence some non-medical users to approach their non-medical experiences with more care.

The impact of the approval of psychedelic psychotherapy on non-medical use patterns is difficult to predict but is not likely to be a major factor in the amount of non-medical use of these drugs. As a result, a higher standard of proof for psychedelic psychotherapy would be difficult to justify based on the possible impact of its approved medical use on non-medical use patterns.

Ethical Aspects of Standards of Proof: The Value of Approving Additional Medications

There are also ethical issues to consider in determining the appropriate standard of proof to use in evaluating medications for psychedelic psychotherapy. The primary consequence of FDA’s use of a standard of proof requiring that the efficacy of a new drug be tested against placebo, instead of in comparison to already available medications, is that a larger number of drugs will be approved for marketing. Demonstrating that a drug performs better on average than an inactive placebo is an easier standard to meet than requiring that a drug be, on average, either equivalent to or more effective than a drug already on the market with some proven degree of efficacy. As Drs. Peter Luria, Curt Furberg and Sidney Wolfe remark, “it is easier to show that your me-too drug is better than nothing than that it is about as good as another drug in the same therapeutic category.”⁹⁵²

When standards higher than comparison to placebo are used, drugs would not be approved if they are more effective than placebo, but still not equivalent or superior on average to currently accepted medications. Yet it is entirely possible that there is a specific subgroup of patients who, for a variety of reasons, would respond better to the drug that wasn’t approved than to the drugs that were more effective on average for larger groups of

⁹⁵¹Halpern J. Hallucinogens, Anesthetic Agents, and Amphetamines in Year 2000. *Pharmacy News*, in press.

⁹⁵²Luria P, Furberg C, Wolfe S. Public Citizen’s Health Research Group. Letter to FDA Documents Management Branch. December 23, 1999. <http://www.citizen.org/hrg/PUBLICATIONS/1503.htm>. The letter comments critically on the Draft Guidance on Choice of Control Group in Clinical Trials, prepared as part of the International Conference on Harmonization (ICH). Released for Consultation at Step 2 of the ICH process on May 7, 1999. The ICH document is published in 64 FR 51767-51780 (September 24, 1999) and is available at <http://www.ifpma.org/ich5e.html#Design>.

patients. An argument could be made that the use of a standard of proof higher than comparison to placebo will unethically deny some patients the medications that are most appropriate for them.

The practical and ethical advantage of approving the maximum number of medicines for various conditions has to do with the fact of individual variability in response to medications in terms of both efficacy and safety. Dr. Temple explains, “There is a real benefit to having more than one treatment of an important condition. Sometimes people are allergic to one member of a drug class, sometimes responses to different members of a class seem to differ among individuals.”⁹⁵³ Dr. Russell Katz, Director of FDA’s Division of Neuropharmacologic Drug Products, voiced a similar concern when he commented on his Division’s approval of a drug for the treatment of Alzheimer’s symptoms that was “pretty much in the same league” as the other two drugs already approved for the same indication. He explained the value of having additional medications available even if they were no more effective on average than other medications, observing, “We just don’t know who’s going to respond to which drug.”⁹⁵⁴

When clinical trials are evaluated, the mean response of the test group is compared with the mean response of the control group or groups. By combining the responses of all the individuals in each of the groups to obtain and compare mean values, specific information about each unique patient is sacrificed in favor of data that will be generally accurate on average for the larger population of subjects from which the sample of the test subjects is drawn. A drug that is inferior and/or riskier on average to another drug may still be more effective and/or safer in some particular patients than the drug that has been found to be superior and/or safer on average. “Our current simplistic statistical concepts of efficacy and safety fail to take this into account,” according to Dr. Wardell.⁹⁵⁵ It is worth recalling here the initial objections voiced by the AMA in opposition to the intention of Congress to grant FDA the authority to regulate efficacy as well as safety. AMA stated, “a drug’s efficacy varies from patient to patient...Hence any judgement concerning this factor can only be made by an individual physician who is using the drug to treat an individual patient.”⁹⁵⁶ With a lower standard of proof and a wider range of drugs on the market, individual patients and their physicians will have a greater opportunity to find the specific drug that works best in their unique situation, especially when the first-line drugs fail.

One approach to providing drugs for all subgroups of patients is to try to identify positive responders in the studies with drugs that have performed worse on average than

⁹⁵³Temple R. When Are Clinical Trials of a Given Agent vs Placebo No Longer Appropriate or Feasible? *Control Clin Trial*18 (1997): 617.

⁹⁵⁴Staff. FDA OKs New Alzheimer's Option. *AP Wire Service* (April 22, 2000). The new drug is called Exelon.

⁹⁵⁵Wardell, Lasagna (1975): 96.

⁹⁵⁶*Ibid.*, 14.

already approved drugs. New studies in the subgroup of positive responders could subsequently be conducted, with the test drug compared to accepted medications for that specific subgroup of patients. Studies of this sort are considered “enrichment designs” in which a study is enriched with patients who have already responded to the test drug or are likely to respond.⁹⁵⁷ Such studies are common. However, enrichment designs have been critiqued on methodological grounds,⁹⁵⁸ and the minimal financial incentives for conducting trials for small patient populations reduces the likelihood that these trials would be conducted in these instances.⁹⁵⁹ Dr. Lasagna has observed, “It is fascinating how few formal attempts have been made to “fine tune” the use of a drug, although the literature contains a large number of retrospective analyses of trials that seemingly have identified patient factors that affected the nature or degree of response to a drug. While some of these post hoc correlations are almost certainly spurious, others are not, and our ability to identify these factors in advance should increase our ability to tailor the choice of drug, and its regimen, to the needs of individual patients.”⁹⁶⁰ Dr. Steven Hyman, Director of the National Institute of Mental Health (NIMH) and Dr. David Shore, Associate Director for Clinical Research, NIMH, acknowledge, “To put it bluntly, at present we do not understand the heterogeneity of mood disorders in a way that allows us to usefully subdivide clinical populations for drug trials.”⁹⁶¹ Dr. Paul Leber, ex-Director of FDA’s Division of Neuropharmacological Drug Products, explains, “it is ordinarily impossible to learn prior to extensive clinical experience with a new drug which, if any, patient characteristics reliably predict a consistent treatment response.”⁹⁶² A standard of proof that approves new drugs if they are better than placebo will provide the entire population of patients with more treatment options than would relying on the identification of patient subgroups who respond well to otherwise inferior new medicines and the subsequent conduct of additional clinical trials in these subgroups seeking to prove the new drugs

⁹⁵⁷Gershon S, Ferris S, Kennedy J, Kurts N, Overall J, Pollack, B, Reisberg B, and Whitehouse P. Methods for the Evaluation of Pharmacologic Agents in the Treatment of Cognitive and Other Deficits in Dementia. in (ed.) Prien R, Robinson D. *Clinical Evaluation of Psychotropic Drugs: Principles and Guidelines*. New York: Raven Press, 1994:467-499.

⁹⁵⁸Leber P, Davis C. Threats to the validity of clinical trials employing enrichment strategies for sample selection. *Control Clin Trials* 19 (Apr 1998) 2:178-87.

⁹⁵⁹FDA’s Orphan Drug program was created to provide financial incentives for the development of drugs for small populations. Nevertheless, the existence of this program does not ensure that studies for small subgroups of patients are ever conducted.

⁹⁶⁰Lasagna L. Clinical trials in the natural environment. *Tufts University Center for the Study of Drug Development, Reprint Series RS 8695*. 1985: 47.

⁹⁶¹Hyman S, Shore S. An NIMH Perspective on the Use of Placebos. *Bio Psychiat* 47 (April 15, 2000) 8: 690.

⁹⁶²Leber (1998): 178.

equivalent or superior to accepted medications in these patient subgroups.

There is one major downside of using the comparison of a new drug against inactive placebo as the standard of proof required for marketing approval. Drugs that are inferior on average in efficacy and/or safety to drugs already available on the market can be approved and, with aggressive marketing or discount pricing, may displace more effective and/or safer drugs. This could result in an overall reduction in public health if those patients for whom the newly approved medication really is inferior are influenced to use it instead of a more effective and/or safer older drug. This possibility is a concern of the Public Citizen's Health Research Group. In a letter Dr. Wolfe sent to CDER Director Dr. Woodcock, he stated, "If they can get away with it, a drug company will always prefer to compare their new drug to a placebo, a comparison which will almost always make their drug appear to have a bigger advantage in effectiveness than it would if compared to known existing therapy."⁹⁶³

Ethical Aspects of Standards of Proof: Placebo Controls When Approved Medications Exist

Drs. Luria, Furberg and Wolfe offer an ethical argument against using a standard of proof that compares new drugs to placebos for a particular clinical indication when one or more medications for that indication have already been approved. They object to the questionable and sometimes unethical nature of conducting a clinical trial in which some patients are randomized to a placebo group when approved treatments for their condition are already available on the market.⁹⁶⁴

This exact situation arose in an early draft of Dr. Abrams' protocol for the study of marijuana in the treatment of AIDS wasting patients, the design of which hadn't given sufficient consideration to the ethical aspects of the protocol.⁹⁶⁵ The initial protocol design called for subjects to be randomized for three months to one of three groups, each receiving marijuana of a different potency; high-THC content marijuana cigarettes (7.9%), medium-THC content marijuana cigarettes (3.95%), and THC-free placebo marijuana cigarettes that had all the THC content removed through the use of an alcohol wash. The rationale for the design was that the use of the placebo condition would provide the most accurate test of whether the subjects administered the medium-THC content marijuana cigarettes or the high-THC content marijuana cigarettes showed a significant improvement in weight gain that could be attributed to the THC-content of marijuana.⁹⁶⁶

⁹⁶³Wolfe S. Director Public Citizen's Health Research Group. Letter to Dr. Janet Woodcock, Director CDER. August 25, 1998. <http://www.citizen.org/hrg/PUBLICATIONS/1453.htm>

⁹⁶⁴Luria, Furberg, Wolfe S. (1999).

⁹⁶⁵For an account of the development of this protocol, minus the story of the ethical oversight, see Abrams D. Medical marijuana: tribulations and trials. *J Psychoactive Drugs*30 (Apr-Jun, 1998) 2:163-9. This author had contributed to the design of the protocol and was responsible for the design feature that was criticized, rightly so, as unethical.

Despite the logic behind the experimental design, the AIDS patients on Dr. Abrams' review board refused to accept the inclusion of the placebo marijuana group. They argued that AIDS wasting was potentially fatal and that there was an approved medication for AIDS wasting, the oral THC capsule. Even though the oral THC capsule had been demonstrated to be only of marginal utility, they argued that it was still better than placebo, making it unethical to randomize patients with a potentially fatal disease to an inactive placebo. As a result of these objections, the protocol design was changed. The placebo marijuana was replaced by a low-THC content marijuana cigarette (2%) which was considered likely to offer a noticeable degree of efficacy somewhat comparable to the oral THC capsule. Though the increased efficacy of the low-dose condition made it statistically less likely that a significant difference would be found between the group receiving the somewhat active "low-dose placebo" marijuana and the groups receiving either the medium-THC or high-THC content marijuana cigarettes, the ethical argument was compelling.⁹⁶⁷ As Dr. Lieberman et al. comment, "a low dose on the dose-response curve can be justified if the percentage of patients expected to respond is meaningfully larger than the percentage expected to respond to placebo."⁹⁶⁸

The statement of Drs. Luria, Furberg and Wolfe objecting to what they consider to be FDA's overemphasis on the use of placebo control groups, quoted at some length, is as follows:

The Draft Guidance on Choice of Control Group in Clinical Trials, prepared as part of the International Conference on Harmonization (ICH), is a clear attempt by the Food and Drug Administration (FDA) to spread its pro-placebo-controlled trial ideology globally...Ethical considerations are treated as subordinate to supposed data collection needs; ethics does not even appear in the critical Table 1, which describes the attributes of the different trial designs...The Draft Guidance is a transparent attempt to legitimize evasions of the clear requirements of the Declaration of Helsinki, which requires that in any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or

⁹⁶⁶There are cannabinoids other than THC in marijuana that could contribute to its therapeutic efficacy. NIDA's marijuana is standardized only on THC content.

⁹⁶⁷As discussed in Chapter 2, this study was never conducted. It was approved by FDA but NIDA refused to provide the marijuana. The design that was finally approved and funded by NIDA involved a three week in-patient study of the pharmacokinetic interaction of marijuana with protease inhibitors in HIV patients who do not suffer from AIDS wasting. The 63rd and final patient was enrolled in the study in May 2000. Data analysis will be completed by July 2000.

⁹⁶⁸Lieberman et al. (1999):32

therapeutic method exists...In addition to its attempts to water down the existing ethical codes, the document places undue emphasis on the supposed needs of regulators and pharmaceutical companies (who together make up the ICH) and places these above the needs of patients or physicians⁹⁶⁹...Most patients and physicians have little need for information addressing whether a new drug for a disease for which there already is an effective therapy is better than nothing; they would like to know whether the new drug is better than the existing drug. But the proposed Guidance would drive clinical trials in the opposite direction. While this may make things easier for regulatory bodies, which can approve drugs simply on the basis of superiority to placebo, and to the pharmaceutical industry, which can more easily prove a new drug superior to placebo than approximately equivalent to a known effective treatment, patients will often not receive optimal medical treatment during the trial. If the researchers are convinced before the trial that the new drug (or placebo) is inferior, the study is unethical and should not take place...The document continues the FDA's longstanding assault on active-controlled trials and does so at a time where there is less clinical and ethical justification for such trials than ever. Rather than challenging investigators to obtain the best possible data using an ethical design, the Draft Guidance subordinates these ethical concerns to the reflexive tendency of some researchers to prefer placebo-controlled studies, to the short-sighted interpretations of drug regulatory authorities bent on approving any drug as long as it is somewhat better than nothing, and to the concerns of the pharmaceutical industry.⁹⁷⁰

The ethical arguments of Drs. Luria, Furberg and Wolfe against the use of placebo controls need to be considered seriously and taken into account. In regard to standards of proof, it is unclear whether they propose that drugs be approved if proven equivalent to an already approved medication, or whether they think that new drugs should be approved only if proven superior to the best alternative treatment. In either case, their argument does

⁹⁶⁹The need to open up the ICH process has been noted by Dr. Paul Booth, who commented, "FDA's approach to implementing the ICH Guidelines, however, has failed to meet the standards for openness and balanced representation that are necessary for ready acceptance of the ICH standards. FDA should redouble its efforts to open the ICH process to participation by groups such as consumers, and to regularly solicit as wide a range of views on the process as possible. This would build public confidence that safety standards were being protected, and help deter legal challenges to U.S. adoption of ICH standards." Booth P. FDA Implementation of Standards Developed by the International Conference on Harmonisation. *Food Drug Law J.* 52 (1997) 2: 223.

⁹⁷⁰Luria, Furberg, Wolfe (1999).

not consider the needs of those patients whose rare or unique responses would cause them to react more positively than the average person with their disease to drugs that may have been shown to be inferior on average in efficacy and/or safety to already approved drugs, but were more effective than placebo in some subgroup of patients. This ethical issue, which is not taken into account by Drs. Luria, Furberg and Wolfe, argues for the use of the lower standard of proof of comparison against placebo if the ethics of conducting clinical trials with placebo groups can be addressed.

Ethics of Placebo Controls in Clinical Studies: When No Approved Medications Exist

Evaluating the ethical aspects of the use of placebo controls in clinical research is a complex matter that will turn on the individual circumstances of each unique clinical trial.⁹⁷¹ The central ethical issue that arises with the use of inactive or active placebo controls involves the failure to treat the condition of those patients who end up in the placebo control group. Medical ethicist Dr. Baruch Brody states this issue as follows, “The crucial concern is that the subjects in the control group are being unfairly denied certain beneficial medical interventions.”⁹⁷²

To simplify, there are four basic situations, 1) the symptoms or condition of the patients are extremely serious and/or life-threatening, with the denial of treatment resulting in irreversible damage, 2) the symptoms or condition of the patients are less serious and present no direct and immediate threat of mortality and no irreversible consequences, 3) there are available treatments with some degree of efficacy for the condition, 4) there are no available treatments with some degree of efficacy for the condition.

When there are no available, approved treatments for the medical condition of the patients in the study, the ethical issue is similar regardless of whether the illness or condition is extremely serious and/or life-threatening with potentially irreversible consequences, or less serious, not life-threatening with no irreversible consequences. When no approved treatments are available, no approved treatments are being denied in a study with a placebo control; as a result allocating patients to a placebo group would be ethical.⁹⁷³

Of course, it is not quite that simple. The sponsor of a study must have some reason to believe that the test drug, device or procedure may prove efficacious for that patient population, or else the study wouldn't be conducted. While there is some probability greater than zero that the test drug will prove effective, that probability could be quite low. Alternatively, there could be a substantial amount of data available about the efficacy of the

⁹⁷¹O'Leary K, Borkovec T. Conceptual, methodological, and ethical problems of placebo groups in psychotherapy research. *Am Psychol* 33 (Sept 1978) 9:821-30.

⁹⁷²Brody B. When are Placebo-Controlled Trials No Longer Appropriate? *Control Clin Trial* 18 (1997): 603.

⁹⁷³ICH Draft Consensus Guideline, Choice of Control Group in Clinical Trials. Section 2.1.3 Ethical Issues, states, “When a new agent is tested for a condition for which no effective treatment is known, there is usually no ethical problem with a study comparing the new agent to placebo.”

test drug, with the trial in question being the final piece of evidence required for FDA approval. An extreme case would be if the treatment was already approved in another country, but not yet in the United States.

Complicating this analysis is the fact that patients assigned to placebo groups in clinical trials frequently report some degree of symptom relief. If there were no placebo effect, there would be no need to use placebos in research. Drs. Greenberg and Fisher reviewed the use of medications in the treatment of depression and reported that “about one-third of patients do not improve with anti-depressant treatment, one-third improve with placebos, and an additional one-third show a response to medication that they would not have achieved with placebos. Thus, with the most positive outlook, about two-thirds of the cases – placebo responders and those who do not respond to anything – would do as well or better with placebo treatment as they would do if treated by an active medication.”⁹⁷⁴

Furthermore, while placebos can also generate side effects, the side effect profile of the placebo is likely to be smaller than that of the treatment being tested.⁹⁷⁵ As a result, patients assigned to the placebo group may have an advantage in terms of safety over subjects assigned to the test group.

How one evaluates the ethical aspects of knowingly allocating some subjects to the placebo group when there are no approved treatments will depend on the degree of uncertainty over the potential efficacy of the new treatment being tested, the risk profile of the treatment, the seriousness of the illness if left untreated for the duration of the clinical trial, and the need for generally accepted scientific data to evaluate the test drug for possible prescription use.

Ethics of Placebo Controls in Clinical Studies: Degrees of Suffering

When some known treatment is available, those patients who will be allocated to the inactive or active placebo control group are clearly being asked to suffer to some degree, at least in the short-run. If the known treatment is only marginally effective, then the denial of treatment to the subjects in the placebo group is of minimal importance, especially if the symptoms are less serious or not life-threatening. If the known treatment is substantially

⁹⁷⁴Greenberg R, Fisher S. Examining Anti-depressant Effectiveness: Findings, Ambiguities, and some Vexing Puzzles. in (eds.) Fisher S, Greenberg R. *The Limits of Biological Treatments for Psychological Distress- Comparisons with Psychotherapy and Placebo*. Hillsdale, New Jersey: Lawrence Erlbaum Associates, 1989: 6-7.

⁹⁷⁵*Ibid.*, 23. “A substance like imiprimine usually initiates clearly defined body experiences (e.g., dry mouth, tremor, sweating, constipation). Inactive placebos used in studies of antidepressants also apparently initiate some body sensations, but these are fewer, more inconsistent, and less intense as indicated by the fact that they are less often cited by patients as source of discomfort causing them to drop out of treatment. (Klein et al., 1980).” Klein D, Gittleman R, Quitkin F, Rifkin A. *Diagnosis and drug treatment of psychiatric disorders; Adults and children*. (2nd Edition). Baltimore: Williams and Wilkins, 1980.

effective and the symptoms are serious and/or life-threatening with the potential of irreversible consequences from not receiving the treatment, the use of inactive or active placebo control groups will be difficult to justify.⁹⁷⁶

Dr. Temple concurs with some criticisms of the use of placebo control groups that Drs. Luria, Furberg and Wolfe raise in general, and also level against him personally as the FDA's primary proponent of placebo trials.⁹⁷⁷ Dr. Temple states, "Where there is good evidence that a particular patient population benefits in terms of improved survival or prevention of irreversible morbidity from a therapy to which they have access, one cannot randomize patients to placebo to test a new drug."⁹⁷⁸

Dr. Temple has expressed the view that patients can give informed consent to the possibility of experiencing discomfort resulting from the lack of symptomatic relief, even when treatments are already available for those symptoms. In his view, "In this case, [known therapy, lack of symptomatic relief] I believe one can almost always use a placebo control because the only consequence to an informed patient of lack of effectiveness is discomfort, something patients can agree to accept. Although the contrary has been suggested, I do not think the Declaration of Helsinki says or means that one must always give people in a trial effective treatment when effective treatment is known to exist."⁹⁷⁹ The ICH Guidelines concur, stating, "it is considered ethical to ask patients to participate in a placebo-controlled trial, even if they may experience discomfort as a result, provided the setting is non-coercive and they are fully informed about available therapies and the consequences of delaying treatment."⁹⁸⁰

Drs. Luria, Furberg and Wolfe agree with Dr. Temple and with the ICH guidelines to some degree, noting, "We would agree that trials of treatments for mild, self-limited conditions such as mild pain or seasonal allergies can use a placebo because the risk to patients is minimal."⁹⁸¹ They continue, however, to argue that, "The Draft Guidance is

⁹⁷⁶ICH Draft Consensus Guideline, Choice of Control Group in Clinical Trials. Section 2.1.3 Ethical Issues, states, "In cases, where an available treatment is known to prevent serious harm, such as death or irreversible morbidity in the study population, it is generally inappropriate to use a placebo control."

⁹⁷⁷Drs. Luria, Furberg and Wolfe state in their letter that, "This sometimes unethical ideology has been laid out in a series of publications by an FDA employee [Dr. Temple] and would take on added force if this poorly thought-out Guidance were finalized and adopted by other ICH countries."

⁹⁷⁸Temple R (1997): 614. See also Temple R. Special study designs: early escape, enrichment, studies in non-responders. *Commun in Stat* 23 (1994):499-531. Temple R. Problems in interpreting active control equivalence trials. *Accountabil in Res* 4 (1996):267-75. Temple R. Difficulties in evaluating positive control trials. *Proceed Am Stat Assoc Biopharmaceut Sec*(1983):1-7.

⁹⁷⁹Temple R (1997): 614.

⁹⁸⁰ICH Draft Consensus Guideline, Choice of Control Group in Clinical Trials. Section 2.1.3 Ethical Issues.

⁹⁸¹Luria, Furberg, Wolfe (1999).

silent on just what constitutes a major health risk. Rather than promoting practices that place patients unnecessarily at risk, the FDA and ICH should formulate a placebo policy that stipulates for specific diseases of particular severities whether and for how long effective therapy can be denied. The FDA and ICH should establish a threshold of acceptable increases in the absolute incidence of adverse events due to the withholding of effective therapy for at least the major clinical syndromes. If, based on previous placebo-controlled trials, withholding therapy can be expected to lead to an excess incidence above that threshold, the placebo would be precluded.”⁹⁸² However, Dr. Leber has observed that there is insufficient evidence to permit the reliable estimation of the likely amount of excess incidence of adverse effects in placebo subjects in psychiatric research. Placebo subjects have even demonstrated “clinically substantial degrees of improvement, albeit not to the same extent as patients assigned to active treatments.”⁹⁸³ In a study of 19,639 patients enrolled in FDA-approved research testing seven new drugs that were approved for the treatment of depression, Dr. Khan and associates observed the surprising finding that, on average, placebo subjects experienced fewer attempted and completed suicides than subjects randomized to the investigational drugs or the active comparators.⁹⁸⁴

The use of rescue medications, in which an active treatment can be administered to subjects if their symptoms cross some predetermined level, can mitigate to some extent the negative health consequences that may arise in patients whose health deteriorates during the course of a placebo-controlled clinical trial.⁹⁸⁵ The use of rescue medications does not inherently break the blind, since all that is needed for the administration of the rescue medication is the worsening of symptoms, regardless of whether the subject was in the test group or the placebo group. Subjects whose health does deteriorate during the course of a clinical trial to an extent sufficient to require a rescue medication may have been randomized to a placebo group, the new medication could have been ineffective in general or just ineffective for that specific patient, or the new medication could have caused negative side effects. Only at the conclusion of the study when the blind is broken should the number of patients on the test drug who received the rescue medication be compared to the number of patients in the placebo group who received the rescue medication.

A major conference seeking consensus on the use of placebo controls in psychiatric research was convened by NIMH and the National Depressive and Manic Depressive Association, an organization promoting the interests of patients. The conference organizers

⁹⁸²Ibid.

⁹⁸³Leber P. The Use of Placebo Control Groups in the Assessment of Psychiatric Drugs: An Historical Context. *Bio Psychiat* 47 (April 15, 2000) 8:700.

⁹⁸⁴Khan A, Warner H, Brown W. Symptom Reduction and Suicide Risk in Patients Treated with Placebo in Antidepressant Trials: An Analysis of the FDA Database. *Arch Gen Psychiat* 57 (Apr 2000) 4:311-7.

⁹⁸⁵ICH Draft Consensus Guideline, Choice of Control Group in Clinical Trials. Section 2.1.5.2.2. Early Escape; Rescue Medication, states, “Early escape refers to prompt removal of subjects whose clinical status worsens...or who have a single event that treatment was intended to prevent.”

concluded that, “the use of placebos in unipolar and bipolar disorders remains scientifically justified; however...research evaluating the potential of alternative non-placebo-controlled designs is indicated.”^{986 987} With more serious conditions for which there are alternative treatments, Dr. Temple suggests a different sort of protocol design. He states, “In some cases, especially where there is toxicity as well as benefit from the older therapy, a dose-response study, using less than fully effective doses of the control and possibly, of the new drug, is another possible approach.”⁹⁸⁸ Yet another option is add-on trials,⁹⁸⁹ in which the new drug is combined with the old drug to see if there are any synergistic effects. A control group can receive the old drug with placebo so that both groups would be blinded as to whether or not they were receiving the new drug as well. This option would be problematic if there were any potentially negative drug-drug interactions.

Though the issue is still contentious, placebo controls can ethically be justified in a wide range of studies, including most of the potential applications for psychedelic psychotherapy.

The Value of Placebo Controls in Clinical Trials

Protocol designs comparing active treatments without a placebo control group have important limitations, due to the fact that placebo responses can be quite large. Drs. Hyman and Shore report, “recent presentations at scientific meetings have described placebo responses in the 30-40% range in disorders such as schizophrenia, major depression, etc.”⁹⁹⁰ The federal Agency for Health Care Policy and Research conducted a meta-analysis of over 80 studies of anti-depressant drugs that were approved by FDA for prescription use and found that the placebo effect averaged 32%.⁹⁹¹ In a recent study of patients with posttraumatic stress disorder (PTSD), the authors report, “The placebo response rate of 32% was comparable with what has been observed in previous multi-center PTSD clinical trials.”⁹⁹² A study of 19,639 subjects enrolled in FDA-approved studies of new

⁹⁸⁶Charney D. The Use of Placebos in Randomized Clinical Trials of Mood Disorders: Well Justified, but Improvements in Design are Indicated. *Bio Psychiat* 47 (April 15, 2000) 8:687.

⁹⁸⁷Ranga K, Krishnan R. Efficient Trial Designs to Reduce Placebo Requirements. *Bio Psychiat* 47 (April 15, 2000) 8:724-726.

⁹⁸⁸Temple (1997): 619.

⁹⁸⁹ICH Draft Consensus Guideline, Choice of Control Group in Clinical Trials. 2.1.5.2.1. Add-on Study, Placebo- Controlled, states, “Such studies are useful when standard therapies are known to decrease mortality or irreversible morbidity, so that the therapy cannot be withheld from a patient population known to benefit from it...This design is useful only when standard therapy is not fully effective.”

⁹⁹⁰Hyman, Shore (2000): 691.

⁹⁹¹Treatment of Depression—Newer Pharmacotherapies: Summary, Evidence Report/Technology Assessment Number 7. Rockville, MD, Agency for Health Care Policy and Research, March 1999. AHCPR Pub. No. 99-E013. <http://www.ahcpr.gov/clinic/deprsumm.htm>

antidepressants found that “symptom reduction was 40.7% with investigational drugs (n = 4,510), 41.7% with active comparators (n = 1,416), and 30.9% with placebo (n = 2,805).”⁹⁹³ The federal Agency for Health Care Policy and Research reviewed more than 80 studies of antidepressants and reported that 50% of the patients on the test drugs improved versus 32% on the placebo.⁹⁹⁴ In studies of patients with acute mania, the placebo response rate averaged 23% and “in studies of acute bipolar depression the placebo response rate is even higher, averaging 29%. These high placebo response rates indicate that alternative trial designs that omit a placebo control group are likely to have limited validity.”⁹⁹⁵

Dr. Temple explains the analytical problem as follows, “The fundamental problem is that in a great many settings, including trials of symptomatic treatments and trials of mortality/morbidity endpoints, an equivalence trial is difficult or impossible to interpret. Such a trial relies on a historical assumption that is not provable and is often not true, namely that the trial as conducted, had assay sensitivity, i.e., that had there been a placebo group present, the active therapies could have been distinguished from placebo *in that trial*. The remedy, in the symptomatic treatment case, is to do a placebo-controlled or placebo- and active-drug controlled trial.”⁹⁹⁶ Dr. Temple expressed the view that equivalence trials could be persuasive if the active control (existing approved drug) had been consistently demonstrated to be more effective than placebo controls in its initial trials, and if the patient population and other study conditions are as similar as possible to the trials in which the active control was compared to the placebo. However, the likelihood that conditions would be similar enough between two trials to make equivalence trials sufficient is called into question by the heterogeneity of patient populations in mental health research.^{997 998} As Kristin Mattocks, MPH, and Dr. Ralph Horwitz stated in their review of the use of placebo control groups in mental health research, “Considering the evidence we have presented in

⁹⁹²Brady K, Pearlstein T, Asnis G, Baker D, Rothbaum B, Sikes C, Farel G. Efficacy and Safety of Sertraline Treatment of Posttraumatic Stress Disorder: A Randomized Controlled Trial. *JAMA* 283 (April 12, 2000) 14:1842.

⁹⁹³Khan A, Warner H, Brown W. (2000): 311.

⁹⁹⁴Goode E. More Fuel for Debate on Prozac. *New York Times, Health and Fitness*(April 25, 2000): D7.

⁹⁹⁵Keck P, Welge J, McElroy S, Arnold L, Strakowski S. Placebo Effect in Randomized, Controlled Studies of Acute Bipolar Mania and Depression. *Bio Psychiat* 47 (April 15, 2000) 8:754.

⁹⁹⁶Temple (1997): 617.

⁹⁹⁷Sources of heterogeneity include disease severity, comorbid psychiatric and medical conditions, seemingly spontaneous onset and remission, use of cotherapies, differential compliance in regard to adhering to medication regime, differential attrition due to breaking the blind regarding assignment to placebo or active agent, and more traditional variations in patient characteristics such as age, gender, socioeconomic status which can persist despite randomization and which can and do differ substantially between trials.

⁹⁹⁸Kunz R, Oxman A. The unpredictability paradox: Review of empirical comparisons of randomized and non-randomized clinical trials. *BMJ* 317 (1998): 1185-1190.

this review detailing the wide variation in response rates within both the placebo and treatment groups, we find it quite likely that active control equivalence trials may not be able to provide persuasive evidence to measure the treatment benefits of a new therapeutic agent.”⁹⁹⁹ Drs. Hyman and Shore affirm that placebo controls are frequently necessary, stating, “we appreciate the concern by federal regulatory agencies that showing “equivalence” between an experimental treatment and a standard treatment may be inadequate to truly establish efficacy, and comparison with placebo is generally needed.”¹⁰⁰⁰ Dr. Leber summarizes the ethical and analytical arguments and concludes, “50 years of experience speak to the unique value and utility of placebo-controlled trials. There is little room for doubt that the continued use of placebo control groups is vital to the protection of the drug supply. Although respect for the interests of individual patients requires that placebo not be used in every setting and when used, used prudently, nothing requires that its use be proscribed absolutely.”¹⁰⁰¹

Economically, placebo-control trials have the advantage of needing fewer subjects than active-control trials to determine efficacy or lack of same.¹⁰⁰² As Drs. Luria, Furberg and Wolfe report, “the pharmaceutical industry...can more easily prove a new drug superior to placebo than approximately equivalent to a known effective treatment.”¹⁰⁰³ They claim, however, that the economic advantage is limited, “In most cases, the differences between the sample sizes required for placebo- and active-controlled trials [testing for equivalence] are modest. One can compensate for this supposed benefit of placebo-controlled trial by recruiting more actively or opening additional study sites, a relatively straightforward practice in this era of multicenter studies and human experimentation corporations (HECs).”¹⁰⁰⁴ Regardless of whether or not the additional number of subjects needed for a comparative study testing for equivalence is modest, many studies comparing two or more treatments are seriously underpowered to determine whether one treatment is superior to another.¹⁰⁰⁵ The

⁹⁹⁹Mattocks K, Horwitz R. Placebos, Active Control Groups, and the Unpredictability Paradox. *Bio Psychiat* 47 (April 15, 2000) 8:697.

¹⁰⁰⁰Hyman, Shore (2000): 691.

¹⁰⁰¹Leber P (2000): 705. see also Leber P. The placebo in clinical trials (a view from the FDA). *Psychopharmacol Bull* 22 (1986): 30-32 ; Leber P. Hazards of inference: The active control investigation. *Epilepsia* 30 (suppl 1) (1989): S57-S63 ; Leber P. Is there an alternative to the randomized controlled trial? *Psychopharmacol Bull* 27 (1991): 3-8 ; Leber P. Challenges to the ethicality of clinical research. *Psychopharmacol Bull* 32 (1996): 11-13.

¹⁰⁰²ICH Draft Consensus Guideline, Choice of Control Group in Clinical Trials.2.1.6.3. Efficiency, states, “Placebo-controlled trials are efficient in that they can detect treatment effects with a smaller sample size than other type of concurrently controlled study.”

¹⁰⁰³Luria, Furberg and Wolfe (1999).

¹⁰⁰⁴Ibid.

conduct of comparative trials designed to determine superiority will entail significant financial and practical burdens over comparison to placebo.

Primarily for reasons of analytical clarity but also due to economic concerns, the use of placebo controls remains ethically justified in most instances in which psychedelic psychotherapy would be evaluated.

Ethical Aspects of Standard of Proof

There is no simple ethical formula for determining whether the standard of proof that should be used to evaluate any form of psychedelic psychotherapy is the minimal standard requiring superiority to placebo, a higher standard requiring equivalence to an approved medication if such a medication does exist, or the highest standard requiring superiority to all approved medications.

A strong ethical argument can be made that patients and physicians should have the widest range of choices through the use of the minimum standard of comparison against placebo. The rights of individuals to access the broadest spectrum of drugs that sponsors of research are willing to develop is the decisive consideration. There are no ethically compelling reasons to require that any form of psychedelic psychotherapy be, on average, equivalent or superior to approved medications.

Where comparison against placebo is clearly unethical, when an accepted drug improves survival or prevents irreversible morbidity, requiring a higher standard in which the psychedelic psychotherapy must be comparable to the accepted drug is clearly ethical. Yet in most research studies of the efficacy of psychedelic psychotherapy, survival or irreversible morbidity is not immediately at stake and placebo controls can ethically be used.

Due to the need to include placebo groups in most clinical trials in order to assess the results accurately, it is ethical to include placebo control groups and could even be considered unethical not to include them. The economic advantages of testing against placebo as compared to active treatment provides an additional argument in favor of the ethics of placebo control groups.

The results of this ethical analysis of the appropriate standard of proof for psychedelic psychotherapy provide further support to the argument that the same standard of proof that FDA uses for the review of other drugs, comparison of new drug to placebo, is appropriate for the review of most uses of psychedelic psychotherapy.

Methodological Issues: History and Function of the Double-Blind Experiment

The double-blind section of this chapter examines the question of whether a scientifically valid and unbiased comparison of psychedelic psychotherapy against placebo, where ethically permissible, is a practical reality, given the problem of conducting a double-blind study with psychedelic drugs.

The early history of the use of placebo controls to produce a double-blind

¹⁰⁰⁵Kazdin A, Bass D. Power to detect differences between alternative treatments in comparative psychotherapy outcome research. *J Consult Clin Psychol* 57 (Feb 1989) 1:138-47.

experiment has been traced to the late 18th and early 19th century. At that time, placebo controls were used as a method of testing whether homeopathy was quackery or a genuine medical treatment.¹⁰⁰⁶ Homeopathy practitioners subsequently took up the practice themselves in their research.¹⁰⁰⁷ The concept of randomization was developed in 1926 by R.A. Fisher¹⁰⁰⁸ and introduced into clinical research in 1931 by Amberson et al.¹⁰⁰⁹ The first use of the double-blind methodology in psychiatric research took place in 1953, in a study evaluating the use of megadoses of vitamin B₃ in schizophrenia, conducted under the direction of Dr. Abram Hoffer.¹⁰¹⁰ Dr. Hoffer later became a prominent LSD researcher¹⁰¹¹ and also an outspoken critic of the double-blind methodology.¹⁰¹²

The primary goal of the randomized, double-blind, placebo-controlled study is to prevent unconscious as well as conscious bias, either for or against the test drug, from contaminating the results of the study.¹⁰¹³ The problem of unconscious bias in research, and the value of the use of double-blind methodology to reduce or eliminate unconscious bias, is discussed in an FDA document as follows:

In clinical trials, bias (a "tilt" in favor of a treatment) can operate like a self-fulfilling prophesy. The hope for a good outcome can skew patient

¹⁰⁰⁶Kaptchuk T. Intentional Ignorance: A History of Blind Assessment and Placebo Controls in Medicine. *Bull Hist Med* 72 (1998): 389-433.

¹⁰⁰⁷Dean M. A Homeopathic Origin for Placebo Controls: 'An Invaluable Gift of God.' *Alt Therap Health Med* 6 (March 2000) 2:58-66.

¹⁰⁰⁸Box J. R.A. Fisher and the design of experiments, 1922-1926. *Am Stat* 34 (1980): 1-7.

¹⁰⁰⁹Amberson J, McMahon B, Pinner M. A clinical trial of sanocysin in pulmonary tuberculosis. *Am Rev Tuberculosis* 24 (1931): 401-435.

¹⁰¹⁰Hoffer A. Double-Blind Studies. *Can Med Assoc J* 111 (Oct. 19, 1974) 8:752. For more information on that study and subsequent developments, see <http://www.naturalhealthvillage.com/newsletter/991215/hoffer.htm>.

¹⁰¹¹Hoffer A, Smith C, Chwelos N, Callbeck M, Mahon M. Psychological response to d-lysergic acid diethylamide and its relationship to adrenochrome levels. *J Clin. & Exper. Psychopath* 20 (1959):125; Chwelos N, Blewett D, Smith C, Hoffer A. Use of d-lysergic acid diethylamide in the treatment of alcoholism. *Quart J Stud on Alcohol* 20 (1959):577; Fogel S, Hoffer A. The use of hypnosis to interrupt and to reproduce an LSD-25 experience. *J Clin Exp Psychopath* 23 (1962):11; Hoffer A. D-Lysergic acid diethylamide (LSD): A review of its present status. *Clin Pharmacol Therap* 6 (March-April 1965): 183-255.

¹⁰¹²Hoffer A. A Theoretical examination of double-blind design. *Can Med Assoc J* 97 (July 15, 1967) 3:123-127; Hoffer A. The Double-Blind Method. *Can Psychiatri Assoc J* 6 (Oct. 2, 1976):449-450.

¹⁰¹³Friedman L, Furberg C, Demets D. *The Fundamentals of Clinical Trials. 2nd Edition.* St Louis: Mosby-Year Book, 1985: 71.

selection so that the treatment group includes a disproportionate number of patients likely to do well whatever their treatment. The same kind of inadvertent bias can lead both patients and investigators to overrate positive results in the treatment group and negative findings among controls, and cause data analysts to make choices that favor treatment. Clinical trials that include such biases are likely to be incapable of assessing drug effect. In conjunction with randomization, a design feature known as "blinding" helps ensure that bias doesn't distort the conduct of a study or the interpretation of its results. Single-blinding consists of keeping patients from knowing whether they are receiving the investigational drug or a placebo. In a double-blind study, neither the patients, the investigators, nor the data analysts [independent raters] know which patients got the investigational drug. Only when the closely guarded assignment code is broken to identify treatment and control patients do the people involved in the study know which is which.¹⁰¹⁴

The FDA Guidance Document, "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" elaborates further on the issue of bias:

Any clinical trial may be subject to unanticipated, undetected, systematic biases. These biases may operate despite the best intentions of sponsors and investigators, and may lead to flawed conclusions. In addition, some investigators may bring conscious biases to evaluations.¹⁰¹⁵

When double-blind methodologies are not used, unconscious bias resulting in an "expectancy effect," in which experimenters find "objective" confirmation for what they expect to be the true nature of the test drug, cannot be ruled out.¹⁰¹⁶ Dr. Robert DeLap, Director of FDA's Office of Drug Evaluation V, observes, "Expectation is a powerful thing. The more you believe you're going to benefit from a treatment, the more likely it is that you will experience a benefit."¹⁰¹⁷

The placebo-controlled, double-blind experimental design is an important tool in the effort to eliminate bias from research. There are many instances in which placebo-controlled, double-blind studies are effective in both theory and practice. In these instances, neither the subjects nor the experimenters can detect any clues that they can use to improve

¹⁰¹⁴Flieger K. Testing Drugs in People. *FDA Consumer: Special Report on New Drug Development in the United States* (January 1995). <http://www.fda.gov/fdac/special/newdrug/testing.html>

¹⁰¹⁵Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products: 4. <http://www.fda.gov/cder/guidance/1397fnl.pdf>

¹⁰¹⁶Barber T. *Pitfalls in human research*. New York: Pergamon Press, 1976.

¹⁰¹⁷Nordenberg T. The healing power of placebos. *FDA Consum* 34 (Jan-Feb 2000) 1:14.

over chance their ability to guess whether a placebo or the test drug was administered to a particular subject at a particular time. Unfortunately, in many studies of traditional psychiatric medications and even more so in psychedelic psychotherapy protocols, double-blind methodologies frequently fail in practice to produce effective double blinds or even single blinds.

Double-Blind Issues in Traditional Psychiatric Research

Given the primary emphasis FDA places on double-blind studies, there are remarkably few papers in the scientific literature devoted to determining whether studies that are designed to be double-blind in name are in fact double-blind in practice. In a successful double-blind, both subjects (single-blind) and experimenters (double-blind) are unaware whether any specific subject has received an active drug or a placebo. Few double-blind studies in the published scientific literature report data concerning whether subjects were asked if they thought they were in the treatment group or the control group, and if they were asked, what responses were given. Out of 12 double-blind studies published in 1982 in the *British Journal of Psychiatry*, one researcher noted that only one reported testing the double-blind by asking patients to guess whether they received the placebo or the active treatment.¹⁰¹⁸ Perhaps even rarer are studies that report any data concerning whether the investigators themselves made any guesses as to which subjects were in the treatment or the control group, and if they did guess, to what extent their guesses proved accurate when the study was completed and the blinds were broken during the data analysis process.

The relatively universal lack of scrutiny as to whether double-blind studies are indeed double-blind is less of a concern for studies in which the test drug is not likely to offer any subjective clues to either subjects or experimenters. Aside from occasional allergic and other very rare reactions, studies of the safety and effectiveness of antibiotics, for example, seem likely to remain blind. On the other hand, studies of drugs that impact mental processes, or have dramatic and unique physical side effects, or even powerful treatment effects, are less likely to remain blind. As one example, FDA's Stella Machado, Ph.D., supervisor of mathematical statistics in CDER's Quantitative Methods Research Staff, reported that one drug under review caused the skin of people who took it to turn a distinctive yellowish/orange, making it impossible to sustain the effort to conduct a double-blind study.¹⁰¹⁹

¹⁰¹⁸Oxtoby A, Jones A, Robinson M. Is your "double-blind" design truly double-blind? *Br J Psychiat* 155 (1989): 700-701.

¹⁰¹⁹personal communication, Dr. Stella Machado, March 3, 2000. Dr. Machado couldn't give any additional information. She wasn't sure if the drug had been approved, in which case further information would be in the public domain, or whether it was either still in the review process or had been abandoned or rejected, in which case all information about the drug would remain proprietary and not available through FOIA or any other means.

In a critical review of the psychotropic drug literature, Dr. Fisher and Dr. Greenberg investigated the operational success of attempts to conduct double-blind studies.¹⁰²⁰ They gathered evidence that demonstrated that the double-blind methodology failed to work as intended in numerous studies with psychoactive drugs. Dr. Fisher and Dr. Greenberg note, “Because taking a placebo is such a discernibly different experience from taking an active drug, the notion that the two conditions are experimentally equivalent is an illusion. It is simply unfair to compare a largely physiologically silent placebo to an active drug.”¹⁰²¹ They also noted, “During the initial phase [of the research], side effects might be particularly revealing, whereas over an extended time period, degree of therapeutic improvement might assume more importance.”¹⁰²² ¹⁰²³ As Dr. Temple has pointed out, “the long-term placebo effect may not be as plausible as short-term.”¹⁰²⁴

Dr. Fisher and Greenberg believe that the widespread failure of the double-blind in numerous studies has resulted in a situation in which “the efficacy of psychotropic drugs has probably been exaggerated.”¹⁰²⁵ ¹⁰²⁶ They report that there are multiple “studies demonstrating [that] the apparent efficacy of psychotropic drugs in research trials decreases progressively as the controls designed to ensure objectivity are made more stringent.”¹⁰²⁷ ¹⁰²⁸

¹⁰²⁰Fisher S, Greenberg R. (eds.) *The Limits of Biological Treatments for Psychological Distress*. Hillsdale, NJ: Erlbaum Associates, 1989.

¹⁰²¹Greenberg R, Fisher S. Suspended Judgement: Seeing through the Double-Masked Designs: A Commentary. *Control Clin Trial* 15 (1994): 245.

¹⁰²²Fisher S, Greenberg R. How Sound is the Double-Blind Design for Evaluating Psychotropic Drugs? *J Nerv Ment Dis* 181 (1993): 347.

¹⁰²³For a paper that demonstrates that different pill sizes and shapes provided sufficient clues to compromise the double-blind in a study comparing five different treatments, see; Haakenson C, Akiyama T, Hallstrom A, Sather MR. Masking drug treatments in the Cardiac Arrhythmia Pilot Study (CAPS). FASHP for the CAPS Investigators. *Control Clin Trial* 17 (Aug 1996) 4:294-303.

¹⁰²⁴Temple R. NIH Workshop on the Medical Utility of Marijuana, February 19-21, 1997, Slide 9, “Choosing Diseases and Endpoints.”

¹⁰²⁵Fisher, Greenberg (1993): 345.

¹⁰²⁶Other researchers have critiqued the work of Drs. Fisher and Greenberg and have defended the validity of anti-depressant studies. See Quitkin F, Rabkin J, Gerald J, Davis J, Klein D. Validity of clinical trials of antidepressants. *Am J Psychiat* 157 (Mar 2000) 3:327-37. This critique nevertheless affirms the importance of addressing the failure of the double-blind and the impact of the placebo effect. The authors conclude, “In order to clarify relative efficacy in drug-psychotherapy contrasts, minimal requirements should include intrastudy placebo calibration, the participation of expert psychopharmacologists and psychotherapists, and rigorous experimental design and measurement. Multisite studies done by mutually monitored collaborating investigators, some with allegiance to psychotherapy and others to pharmacotherapy, that result in findings repeated at different sites would be most convincing.”

¹⁰²⁷*Ibid.*, 345.

¹⁰²⁹ Though of uncertain relevance to research conducted more recently, a review of 490 antidepressant trials conducted before 1969 concluded that the primary variable that influenced outcome was not the drug being studied but the research methodology that was employed.¹⁰³⁰ A more recent meta-analysis found that studies that did not report even an effort at double-blinding produced treatment effects that were larger than in studies that did try to use the double-blind methodology.^{1031 1032}

In a study that demonstrates bias in a particularly persuasive manner, 22 double-blind studies were reviewed in which a new antidepressant was compared to both an inactive placebo and an older drug that had already been shown to be effective for that same clinical indication. The efficacy of the older drug was then compared with the efficacy found in the earlier, initial trials of that same drug. The hypothesis of the researchers was that the efficacy for the older drug would be lower when it was tested against a newer drug than in its initial trials when it was considered the latest and best drug being tested, when experimenter enthusiasm would be expected to be higher. Effect sizes for the older drug in the newer studies were only one-half to one-quarter of the effect sizes in the initial trials.¹⁰³³ Though the characteristics of the patient populations may have been somewhat different between the initial trials and the subsequent trials, the substantial drop-off in efficacy as measured in the newer studies was attributed at least in part to the reduction in investigator bias in favor of the efficacy of the test drug.

There is at least a theoretical solution to the failure of the double-blind methodology in studies comparing psychotropic drugs to inactive placebos. Inactive placebos need to be replaced with the use of active placebos that have somewhat similar side-effect profiles to the drugs they are being tested against, but without any therapeutic potential. Whether such

¹⁰²⁸There is also a small body of literature on failures to properly randomize subjects between groups. For just one example, see Schulz K. Subverting randomization in controlled trials. *JAMA* 274 (Nov 8 1995)18:1456-8.

¹⁰²⁹Ross M, Olsen J. An expectancy-attribution model of the effects of placebos. *Psychol Rev*88 (1981): 408-437.

¹⁰³⁰Smith A, Traganza E, Harrison G. Studies on the effectiveness of antidepressant drugs. *Psychopharmacol Bull* 5 (1969): 1-53.

¹⁰³¹Schulz K, Chalmers I, Hayes R, Altman D. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 273 (Feb 1, 1995) 5:408-12.

¹⁰³²The fact that a subject's awareness of participating in a study can influence the outcome of the study is known as the Hawthorne effect. For a recent study that attempted to measure the magnitude of the Hawthorne effect, see De Amici D, Klersy C, Ramajoli F, Brustia L, Politi P. Impact of the Hawthorne effect in a longitudinal clinical study. The case of anesthesia. *Control Clin Trial* 21 (Apr 2000) 2:103-14.

¹⁰³³Greenberg R, Bornstein R, Greenberg M, Fisher R. A Meta-Analysis of Antidepressant Outcome Under "Blinder" Conditions. *J Consult Clin Psychol* 60 (1992): 664-669.

substances can indeed be identified in practice is another matter. There are no obvious examples of such active placebos for psychedelic drugs. According to Dr. Greenberg and Dr. Fisher, “Without question, mastery of the active placebo dilemma is central to rescuing the integrity of the double-blind.”¹⁰³⁴

Unfortunately for the design of psychedelic research protocols, the strategy of using an active placebo whose side effect profile matches that of the test drug isn't very effective. This approach reduces only some of the subjective clues that permit subjects and researchers alike to identify who has received the psychedelic drug. Traditional psychiatric drugs are meant to be taken on a daily basis and exert their therapeutic effects gradually and consistently over extended periods of time measuring months and even years. The therapeutic use of psychedelic drugs involves an acute intervention lasting several hours or an entire day that can be powerful, unmistakable and overwhelming. The side effect profile of psychedelic drugs pales before the intended effect of these substances, which no active placebo matched only on side effects but without similar therapeutic effects can adequately mimic. The active placebo solution for the problem of the piercing of the double-blind in traditional psychiatric research thus fails to resolve the issue. The question remains how best to remedy the failure of the double-blind to stay truly blinded in psychedelic research in order to eliminate or minimize bias from compromising the data that is gathered.

The Double-Blind in Psychedelic Research

In practice, the dramatic and profound subjective effects of psychedelic drugs make it exceedingly difficult to blind the subjects as well as experienced researchers/therapists as to whether a full dose of a psychedelic drug or an inactive placebo has been administered. As Dr. Eric Kast stated in a report on a study he conducted in which a single dose of 100 micrograms of LSD (a moderately strong dose) was administered to 80 patients with terminal malignant disease, “No placebo control was used because of the obvious and immediate differentiation of LSD from placebo by the patient as well as the observer.”¹⁰³⁵

¹⁰³⁶ A study explicitly designed to evaluate reactions to an inactive placebo as compared to
¹⁰³⁴Fisher, Greenberg (1993): 348.

¹⁰³⁵Kast E. A Concept of Death. *Psychedelics- The Uses and Implications of Psychedelic Drug*, (eds.) Aaronson B, Osmond H. Garden City, New York: Anchor Books, 1970: 374. Dr. Kast reported that “LSD is not only capable of improving the lot of pre-terminal patients by making them more responsive to their environment and family, but it also enhances their ability to appreciate the subtle and aesthetic nuances of experience...[The LSD experience] not only gives aesthetic satisfaction, but creates a new will to live and a zest for experience that, against a backdrop of dismal darkness and preoccupying fear, produces an exciting and promising outlook...In summary, the drug effect consisted of a lessening of the patients' physical distress and a lifting of their mood and outlook that lasted about ten days.”

¹⁰³⁶For additional information on the use of psychedelic psychotherapy in the treatment of terminal patients, see Kast E. Attenuation of anticipation: a therapeutic use of lysergic acid diethylamide.*Psychiatr Q* 41 (Oct 1967) 4:646-57; Kast E. LSD and the dying patient. *Chic Med Sch Q* 26 (Summer 1966)

LSD found that “the reactions of placebo subjects in the present study did not simulate the effects of the drug.”¹⁰³⁷ The placebo subjects, who were not told that they might receive a placebo, mostly reported somatic, rather than affective or cognitive reactions.¹⁰³⁸ The ability of the experimenters to determine which subjects received the placebo was described as “inevitable.”¹⁰³⁹ Another study comparing LSD to placebo found that placebo reactions tended to be time-sensitive, with the peak of the placebo effect occurring within the first hour.¹⁰⁴⁰ Dr. Hoffer has commented, “There is one good therapy for alcoholism, LSD, which will never be double-blinded.”¹⁰⁴¹

The inability to sustain either a single or a double-blind is not limited to LSD but generalizes to other psychedelic drugs. A recent pilot study investigated the anti-depressive effects of ketamine in patients with depression. The study was reported to be “the first placebo-controlled, double-blinded trial to assess the treatment effects of a single dose of an N-methyl-D-aspartate (NMDA) receptor antagonist in patients with depression.”¹⁰⁴² All seven patients in the study were treated on two separate occasions, during which they were randomly administered either a single moderate dose of .5 mg/kg of ketamine, or an inactive placebo. Though the study was reported to be double-blind, the lead author acknowledged that, “Basically, all subjects and raters knew when active [ketamine] versus [inactive] placebo were administered.”¹⁰⁴³

Of course, given the remarkably powerful range of subjective effects of moderate to full doses of a psychedelic drug, it should be relatively easy for subjects and/or experimenters to determine whether an inactive placebo or a fully active dose of a

2:80-7; Pahnke W, Kurland A, Goodman L, Richards W. LSD-assisted psychotherapy with terminal cancer patients. *Curr Psychiatr Ther* 9 (1969):144-52 ; Pahnke WN, Kurland AA, Unger S, Savage C, Grof S. The experimental use of psychedelic (LSD) psychotherapy. *JAMA* 212 (Jun 1970)11:1856-63; Grof S, Goodman L, Richards W, Kurland A. LSD-assisted psychotherapy in patients with terminal cancer. *Int Pharmacopsychiatry* 8 (1973) 3:129-44 ; Kurland A. LSD in the supportive care of the terminally ill cancer patient. *J Psychoact Drug* 19 (Oct-Dec 1985) 4:279-90.

¹⁰³⁷Linton H, Langs R. Placebo Reactions in a Study of Lysergic Acid Diethylamide (LSD-25). *Arch Gen Psychiat* 6 (May 1962) 5:373.

¹⁰³⁸Ibid., 379.

¹⁰³⁹Ibid., 380.

¹⁰⁴⁰Abramson H, Jarvik M, Levine A, Kaufman M and Hirsch M. Lyergic Acid Diethylamide (LSD-25): The Effects Produced by Substitution of Tap Water Placebo. *J Psychol*40 (1955): 367-383.

¹⁰⁴¹Hoffer A. A Theoretical examination of double-blind design. *Can Med.Assoc J*97 (July 15, 1967) 3:126.

¹⁰⁴²Berman R, Cappiello A, Anand A, Oren D, Heninger G, Charney D, Krystal J. Antidepressant effects of ketamine in depressed patients. *Biol Psychiat*47 (Feb 15, 2000) 4:351.

¹⁰⁴³personal communication, Dr. Robert Berman, April 4, 2000.

psychedelic drug has been administered. More difficult would be determining whether an active placebo of some sort, perhaps a stimulant like Ritalin, or an active but low dose of the psychedelic drug had been administered, with greater chances for uncertainty associated with lower doses of the psychedelic drug.

In practice, numerous psychedelic psychotherapy research studies using a variety of active controls have also failed to achieve an effective double-blind. For example, Dr. Van Dusen and associates conducted a study examining the therapeutic potential of LSD in the treatment of alcoholism, in which scopolamine was used as an active control for LSD.¹⁰⁴⁴ The double-blind was considered to be ineffective.¹⁰⁴⁵ In another study, Dr. Smart and associates evaluated the use of LSD in thirty alcoholics, with ten subjects receiving LSD, ten receiving 60 mg of ephedrine as an active control, and ten receiving the same preparation and psychotherapy but without the drug session. Ephedrine is a stimulant that produces some of the same physical symptoms as LSD. Nevertheless, the double-blind was considered a failure, since 19 out of the 20 therapists involved in the study could identify which patients had received which drug.¹⁰⁴⁶ An FDA and NIMH-funded study conducted in 1968 by Dr. Solomon Snyder compared 1.5 mg of a relatively little known psychedelic drug called DOET, which is somewhat similar to MDA, with 10 mgs of d-amphetamine, and found them to be distinguishable. According to Dr. Snyder, "In the double-blind comparison of DPET and amphetamine they were clearly distinguishable, both in subjective effects and in their effects on the performance of several psychological tests."¹⁰⁴⁷

The experimental design most likely to produce uncertainty is when subjects have been led to expect that they would receive either a psychedelic drug or an inactive placebo, but then were actually administered an active placebo. Just such an experiment was conducted by Dr. Walter Pahnke in 1962, as part of his Harvard dissertation conducted under the direction of his faculty sponsor, Dr. Timothy Leary.¹⁰⁴⁸ Dr. Pahnke's experiment

¹⁰⁴⁴Van Dusen W, Wilson W, Miners W, Hook H. Treatment of alcoholism with lysergide. *Q J Stud Alcohol* 28 (1967) 2:295-303.

¹⁰⁴⁵Ibid.

¹⁰⁴⁶Smart R, Storm T. The efficacy of LSD in the treatment of alcoholism. *Q J Stud Alcohol*(1964) 25:333-338; see also Smart R, Storm T, Baker E, Solursh L. A controlled study of lysergide in the treatment of alcoholism. 1. The effects on drinking behavior. *Q J Stud Alcohol* 27 (Sep 1967) 3:469-82. Smart R, Storm T, Baker E, Solursh L. A controlled study of lysergide. *Q J Stud Alcohol* 28 (Jun 1967) 2:351-3.

¹⁰⁴⁷Snyder S, Weingartner H, Faillace L. DOET (2,5-dimethoxy-4-ethylamphetamine) and DOM (STP) (2,5-dimethoxy-4-methylamphetamine), New Psychotropic Agents and Their Effects in Man. in Efron D. (ed.). *Psychotomimetic Drugs- Proceedings of a Workshop organized by the Pharmacology Section, Psychopharmacology Research Branch, National Institute of Mental Health, held at the University of California, Irvine, on January 25-26, 1969.* Workshop Series of Pharmacology Section, National Institute of Mental Health No 4. New York: Raven Press, 1970: 263.

involved twenty divinity students from Andover Newton Theological Seminary, half of whom received a high dose of psilocybin while the other half received nicotinic acid as an unexpectedly active control substance. This was done in order to "potentiate suggestion in the control subjects, all of whom knew that psilocybin produced various somatic effects, but none of whom had ever had psilocybin or any related substance before the experiment."¹⁰⁴⁹ Nicotinic acid acts more quickly than does psilocybin and produces general relaxation and a warm flush through vasodilation of blood vessels in the skin.

The experiment took place at Marsh Chapel on the campus of Boston University, during the course of a Good Friday service led by Rev. Howard Thurman, a mentor of Dr. Martin Luther King. The purpose of the experiment was to determine whether a psychedelic drug could help catalyze a religious experience in people who were religiously inclined and were taking the substance in a religious context. What follows is an account from one of the subjects describing how he was finally able to determine whether he had been administered either the psilocybin or the placebo. The interview was conducted by this author about twenty-five years after the original experiment had taken place.¹⁰⁵⁰

This account is based on a group experience in which both experimental and control subjects were administered their drugs in the same location at the same time, enabling the subjects to discuss the contents of their subjective experiences with each other during the acute phase of the experiment. As a result, this example does not completely apply to an experimental design in which a single subject in isolation is administered either a test drug or a placebo. However, in some psychedelic therapy research protocols, post-treatment follow-up may involve group therapy that includes members of both the experimental and control subjects. These group therapy sessions provide ample opportunities for subjects to compare notes about their experiences, thus facilitating the delayed determination as to the actual substance each subject had been administered. The following example, while not directly applicable to all research designs, nevertheless serves to illustrate the difficulties inherent in the attempt to keep subjects unaware as to whether they have received an active placebo or a psychedelic drug.

After about a half hour I got this burning sensation. It was more like indigestion than a burning sensation. And I said to T.B., "Do you feel anything?" And he said, "No, not yet." We kept asking, "Do you feel anything?" I said, "You know, I've got this burning sensation, and it's

¹⁰⁴⁸Pahnke W. *Drugs and Mysticism: An Analysis of the Relationship between Psychedelic Drugs and the Mystical Consciousness*. Unpublished doctoral thesis in the History and Philosophy of Religion submitted to Harvard University in 1963.

¹⁰⁴⁹*Ibid.*, 89.

¹⁰⁵⁰Doblin R. The Good Friday Experiment- A twenty-five year follow-up and methodological critique. *J Transper Psychol* 23 (1991) 1:1-28.

kind of uncomfortable." And T.B. said, "My God, I don't have it, you got the psilocybin, I don't have it." I thought, "Jeez, at least I was lucky in this trial. I'm sorry T.B. didn't get it, but I'm gonna' find out." I figured, with my luck, I'd probably get the sugar pill, or whatever it is. And I said to Y.M., "Do you feel anything?" No, he didn't feel anything. So I sat there, and I remember sitting there, and I thought, "Well, Leary told me to chart my course so I'm gonna' concentrate on that." And I kept concentrating and sitting there and all I did was get more indigestion and uncomfortable.

Nothing much more happened and within another 40 minutes, 45 minutes, everybody was really quiet and sitting there. Y.M. was sitting there and looking ahead, and all of the sudden T.B. says to me, "Those lights are unbelievable." And I said, "What lights?" He says, "Look at the candles." He says, "Can you believe that?" And I looked at the candles, and I thought, they look like candles. He says, "Can't you see something strange about them?" So I remember squinting and looking. I couldn't see anything strange. And he says, "You know it's just spectacular." And I looked at Y.M. and he was sitting there saying, "Yeah." And I thought, "They got it, I didn't." ¹⁰⁵¹

Dr. Pahnke was able to sustain the double-blind successfully through all of the preparation phases of the experiment up to and including ingestion of the capsule. The double-blind was even sustained for a portion of the Good Friday service itself because of the use of nicotinic acid as an active placebo. Subjects in the placebo group mistakenly concluded, in the early stages of the experiment, that they were the ones who had received the psilocybin.¹⁰⁵² The group leaders, unaware that an active placebo was going to be used, were also initially unable to distinguish whether subjects had received the psilocybin or the placebo. Psilocybin's powerful subjective effects were eventually obvious to all subjects who received it, even though they had not previously ingested the drug or anything similar to it.¹⁰⁵³ Inevitably, the double-blind was broken during the service as the psychoactive effects of the psilocybin deepened and the physiological effects of the nicotinic acid faded. At the end of the day of the experiment, all subjects correctly determined whether they had received the psilocybin or the placebo even though they were never told which group they were in.¹⁰⁵⁴ In virtually all cases, members of the experimental team were also able to tell which subjects had received the psilocybin and which had received the placebo. Dr. Leary noted, "It was easy to tell who had taken the psychedelics."¹⁰⁵⁵ Dr. Pahnke himself

¹⁰⁵¹Ibid., 5-6.

¹⁰⁵²Pahnke (1963): 212.

¹⁰⁵³Ibid., 212.

¹⁰⁵⁴Ibid., 210.

remained technically blind until after the six-month follow-up, when he finally looked at the code to determine which subjects were in which group.

Subsequent to the completion of the Good Friday Experiment, Dr. Pahnke realized that every single subject had been able to determine whether he had received the placebo or the psilocybin. Clearly, his choice of nicotinic acid had failed to ensure an effective double-blind study. He then undertook a series of additional studies investigating the use of psilocybin in normal volunteers, administering the drug in the non-religious, relatively sterile environment of the Massachusetts Mental Health Center.¹⁰⁵⁶ The primary aim of these studies was “to determine the most useful psychoactive control substance for use with psilocybin.”¹⁰⁵⁷

A total of 40 subjects who had never taken a psychedelic drug were tested in groups of four. In a double-blind randomized manner, most subjects were administered either a high dose of psilocybin (30 or 40 mg), a low dose of psilocybin (9 or 12 mgs) as one active control, or a combination of 20 mgs of d-amphetamine and 130 mg amobarbital (Dexamyl) as another active control. The setting for all subjects was identical, the group listened to “a six hour program of classical music in a supportive environment with psychiatric supervision provided by the experimenters.”¹⁰⁵⁸

The experiment was a partial success. In about three out of four cases, the experimenters could not determine during the course of the experimental session which subject had received which drug or dose. Almost all subjects failed to determine which dosage they had been administered. Both the low dose of psilocybin and the combination of d-amphetamine/amobarbital produced a mild subjective experience, though not the sort of psychedelic peak experience that the higher dose of psilocybin produced. These two substances were considered equally valuable as control substances. Several subjects received a very low dose of 5 mg. of psilocybin, the effect of which was so mild that it could easily be distinguished by both subjects and experimenters from the high dose of psilocybin. Afterwards, however, the experimenters could determine which subjects received which drug or dosage through the review of the questionnaires and individual written accounts.

In this experiment, Dr. Pahnke sought to minimize interaction between the subjects and the experimenters, with the subjects listening to music with as much undivided attention as they could manage. It is unlikely that this practice would be followed in a psychotherapy study. If the goal of a psychedelic research project is to maximize therapeutic outcome,

¹⁰⁵⁵Leary T. *High Priest*. Berkeley: Ronin Press, 1984: 311.

¹⁰⁵⁶Pahnke W, Salzman C. Report on a pilot project investigating the pharmacological effects of psilocybin in normal volunteers. Massachusetts Mental Health Center. Unpublished manuscript, (1966): 1-5.

¹⁰⁵⁷*Ibid.*, 1.

¹⁰⁵⁸*Ibid.*, 2.

therapists would be interacting with subjects in order to take advantage of the ability of the psychedelic state of mind to bring issues of concern to the surface, permitting them to be worked through and resolved. These interactions between therapists and patient would provide more opportunities for subtle clues to assist the therapists, and perhaps also the subjects, in guessing which test substances in which amounts had been administered. While it is entirely possible that some patients in psychedelic psychotherapy studies would remain contentedly listening to music for six hours or so, this would be the exception and not the rule, and therapists would still be checking in periodically with the patient in order to assess their state of mind.

The most important finding of this study in terms of the conduct of double-blind studies is that it demonstrated that drug-naïve subjects as well as experienced investigators have difficulties distinguishing between a medium and a high dose of the same psychedelic drug as long as contact between subjects and experimenters is minimized.

Informed Consent and the Double-Blind

In addition to the inherent difficulties in conducting double-blind studies with psychedelic drugs, federal regulations require that experimenters obtain fully informed consent from human subjects participating in experimental research. This requirement makes it even more difficult to conduct a successful double-blind experiment, since the federal regulations governing informed consent require that a certain minimum set of clues about what to expect from any test drug be provided to subjects in the context of the written informed consent form. According to federal regulations, the informed consent form must include a “description of any reasonable foreseeable risks or discomforts to the subject.”¹⁰⁵⁹ The informed consent form can be somewhat vague and brief about the possible range of expected effects from the test drug, but some accurate set of expectations must be provided to subjects. Deception in research and incomplete disclosure in informed consent forms is permitted in exceptional circumstances, but such deceptions are usually about the exact purpose of the experiment or about certain measures that are being taken during the course of the study, not about the “risks or discomforts” that the subject may experience.¹⁰⁶⁰

The ability of psychedelics to catalyze psychological processes that can bring to the surface difficult and/or repressed emotions is a key factor in their therapeutic potential. Subjects therefore need to be informed that the power of psychedelics is such that difficult or repressed emotions can come to awareness and may be a challenge to deal with, at least initially. Whether or not these emotions are processed in a healing manner depends in part on the courage and honesty of the subject, on the skill of the therapist, and on the preparation the subject has received. As Dr. McEvoy and Keefe make clear, “The

¹⁰⁵⁹45 CFR 46.116 (a) (2). Part 46 - Protection of Human Subjects, Subpart A - Basic HHS Policy for Protection of Human Subjects.

¹⁰⁶⁰Levine R. *Ethics and Regulation of Clinical Research-2nd Edition*. Baltimore: Urban and Schwarzenberg, 1986: 117. See also Chapter 9, Deception.

investigator is obliged to tell patients, based on reasonable projections, the chances that bad outcomes may ensue from research participation and what these possible bad outcomes are.”¹⁰⁶¹ Information in the informed consent form about the possible range of emotions that can be catalyzed by psychedelics makes it easier for subjects to recognize the core attributes of the psychedelic experience, attributes that inactive or active placebos generally do not closely mimic.

MDMA/PTSD Study by Jose Carlos Bouso, Psychology Ph.D. Candidate

The informed consent form to be used by Jose Carlos Bouso, Ph.D. Candidate, University Autonoma de Madrid, in the Spanish Ministry of Health-approved MDMA/PTSD study, is quite descriptive of what subjects may expect to experience if they receive the MDMA instead of the inactive placebo. The informed consent form describing the MDMA experience is as follows:

MDMA is classified as a stimulant of the central nervous system. When consumed without appropriate medical supervision in recreational contexts or when they are abused, stimulants can produce sleeplessness, nervousness, anxiety, muscular tension, increased heart rate and blood pressure, palpitations, dizziness, fever, dryness of mouth, visual difficulties, chest pain, sweating, nausea, and vomiting. Psychotic effects have been described in which hallucinations (perceptual changes) and paranoia appear. Severe negative effects have also been described, especially in cases of consumption of high or toxic doses. Symptoms that may appear in these cases include high fever, muscular pain, loss of consciousness, convulsions, arrhythmia, chest pain and heart attack. These severe effects have resulted in death in some cases. As mentioned above, these undesirable effects can appear when stimulants are taken without proper medical supervision, when dosages are not monitored, or when they are taken by people with pre-existing medical conditions.

When MDMA is administered to physically healthy patients in a controlled clinical context, it tends to produce what could be called a paradoxical effect when compared to the normal effect of stimulants. MDMA's effects are: elimination of anxiety, positive mood, improved capacity for communicating with others and for accessing feelings and memories, and elimination of fear of speaking about traumatic facts or experiences from the past - without producing most of the effects associated with stimulants set forth above. In fact, before it was

¹⁰⁶¹McEvoy J, Keefe R. Informing Subjects of Risks and Benefits, in (ed.) Pincus H, Lieberman J, and Ferris S. *Ethics in Psychiatric Research- A Resource Manual for Human Subjects Protection*. Washington, DC: American Psychiatric Association, 1999: 139.

prohibited, MDMA was used to help patients analyze their problems in a state of serenity and lucidity in which they were better able to gain access to their traumatic memories without losing control of their emotions or actions, yet alleviating the fear or anxiety that is produced when these types of feelings are accessed. The dosage that you will receive may produce secondary effects such as muscular trembling, changes in heart rate and blood pressure, fatigue after the session, and insomnia. The other effects of stimulants described above are rarely produced.¹⁰⁶²

With the information provided above, it is reasonable to assume that most patients should have little difficulty determining whether they received the MDMA or the inactive placebo. Somewhat helpful to the goal of producing an effective double-blind experiment is that the list of adverse effects from the non-medical use of stimulants is remarkably diverse, ranging from anxiety and nervousness to heart attack and death. In addition, some of the acute side effects that are mentioned as possibly resulting from the ingestion of MDMA in clinical research, such as muscle trembling and changes in heart rate and blood pressure, are broadly stated and could be generated by subjects who receive the placebo but are anxious about participating in the experiment.¹⁰⁶³ It is also possible that some of the primary effects of MDMA listed in the informed consent form could be experienced by placebo subjects who feel sufficiently comfortable to work on resolving their traumas during the experimental session. Even the low dose of MDMA that is being used in the study, 50 mgs, produces a noticeable psychological effect, but not one that is considered sufficient for substantial psychological processing.¹⁰⁶⁴ Prior to the experimental session, subjects will be told which dose of MDMA they may receive if they do not receive the placebo. Subjects will be looking for more subtle signs of activity if they are in the initial low-dose groups.

In order to test the effectiveness of the inactive placebo in the context of the double-blind methodology, outcome measures to be used in this study will ask subjects to report whether they thought they received either a placebo, or a low, medium or high dose of MDMA. The therapeutic research team will also record their own guesses as to whether their subjects received MDMA or placebo, with the guesses evaluated for accuracy at the

¹⁰⁶²Bouso J. Informed Consent Form, Spanish Drug Agency Code Protocol # 99-0309. Administration of 3,4-methylenedioxy-methamphetamine (MDMA) to Women with Chronic Post Traumatic Stress Disorder (PTSD) as a Consequence of Sexual Assault. A Dose-Finding Pilot Study. Biological Psychology and Health Department, Faculty of Psychology. Universidad Autónoma de Madrid, Hospital Psiquiátrico de Madrid.

¹⁰⁶³Side effect profiles of placebo have been found to mimic the side effect profiles of active drugs. Ross M, Olsen J. An expectancy-attribution model of the effects of placebos. *Psychol Rev* 88 (1981): 408-437.

¹⁰⁶⁴Adamson S, Metzner R. The Nature of the MDMA Experience and its Role in Healing, Psychotherapy, and Spiritual Practice. *Revision* 10 (Spring 1988) 4:59-72.

conclusion of the study.

The Psilocybin/OCD Study by Dr. Francisco Moreno and Dr. Pedro Delgado

Dr. Francisco Moreno and Dr. Pedro Delgado, University of Arizona, have been approved by the FDA to study the use of psilocybin in a maximum of ten patients with obsessive-compulsive disorder. Their informed consent form is illustrative of the sort of information that is considered appropriate to provide to experimental subjects who are patients in need of treatment.

1) Psilocybin is a hallucinogenic/psychedelic drug. At the higher doses, psilocybin can cause severe distortion in all body sensations and thinking. This can include abnormal perception in all senses such as visual changes, visual hallucinations, hearing changes and auditory hallucinations, abnormal smells or bodily sensation, and an unusual mixing of sensations where for example sounds may be perceived as pictures or images or colors could be perceived as tastes. These experiences are usually accompanied by intense changes in mood states. This can include elation or euphoria, anxiety and panic feelings, or depressive feelings. Emotions can change quickly from one to another. While these experiences are described by most people as pleasant or profound, to some it may be frightening and include symptoms of panic, depression, and confusion. The symptoms listed above usually begin within the first hour after taking the psilocybin and can last for up to 12 hours, although most people find that these symptoms are gone by 6 hours after ingestion.

Psilocybin will also cause dizziness, nausea, vomiting, headaches, increased pulse and blood pressure, dilated pupils, slightly elevated temperature, raising of skin-hair, and increased reflexes. These symptoms usually begin 20 to 30 minutes after taking the drug and can last up to 6 hours.¹⁰⁶⁵

The broad range of effects listed above include some that are usually unique to psilocybin, such as “visual hallucinations, hearing changes and auditory hallucinations, abnormal smells or bodily sensation, and an unusual mixing of sensations,” along with a variety of other effects, such as increased blood pressure and pulse, and nausea, that could just as easily be produced by anxiety and the “placebo effect.” Subjects who failed to experience any of the distinctive effects they are told can be caused by psilocybin would have an increased chance of guessing accurately that they received the placebo. The degree of detail provided about the psilocybin experience in the informed consent form suggests

¹⁰⁶⁵Subject’s Consent Form, IND # 56,530. <http://www.maps.org/research/psilo/azconsent.html>

that most subjects would be able to distinguish medium or high doses from either active or inactive placebo, and would probably also be able to distinguish medium or high doses from a low dose of psilocybin just above the threshold level for psychoactivity.

Proposed Study of LSD in Cancer Patients by Richard Yensen Ph.D. and Dr. Donna Dryer

Richard Yensen, Ph.D. and Dr. Donna Dryer, Orenda Institute, Baltimore, Maryland, are still in the protocol development and approval stage for a study that is intended to evaluate the use of LSD-assisted psychotherapy in the treatment of anxiety, depression and pain in cancer patients. This study is designed to build on the research with LSD in cancer patients that was conducted at Spring Grove in the late 1960s and early 1970s.¹⁰⁶⁶ As this study is presently designed, subjects will be randomized into one of three groups and will receive either a very low dose of LSD of 10 micrograms, intended to be below threshold or barely perceptible, or a significant and catalytic dose of 150 micrograms, or a quite large dose of 400 micrograms which is intended to produce an overwhelming psychedelic peak experience.

The portion of their detailed informed consent form that describes the acute effects of LSD is as follows:

The actions of LSD, like that of other drugs affecting the brain-mind system, are complex in nature and are not yet completely understood. From session to session of LSD psychotherapy and at different times within the same session, various physiological rhythms, such as your pulse, may temporarily go up or down. These physiological effects seem to reflect the emotional nature of the particular experience rather than the actual effect of LSD. The emotional responses during LSD psychotherapy sessions vary from person to person and may include fear and anxiety as well as tranquility and serenity. During the course of your therapy, you may experience rare transient occurrences, reminiscent of the experiences that occurred during the LSD session(s).

During the LSD psychotherapy sessions, you may experience any of the following: transient pains, occasional nausea, vomiting, coldness, sweating, blurred vision. There may also be perceptual changes involving hearing, vision, touch, taste, smell and/or other body sensations. Your awareness of space and time may be altered. You may experience periods of intense emotion such as crying or laughing. In rare instances a transient, psychotic-like state may occur, including feelings of panic and paranoid thinking.

[Subjects need to sign the following statement indicating that they understand the information presented to them in the consent form.]

¹⁰⁶⁶See Chapter 1 for a discussion of the Spring Grove research projects.

My therapist and cotherapist will be present throughout the LSD psychotherapy session, which will last at least 8-12 hours. Throughout most of the LSD psychotherapy session, I will recline on a couch or bed with my eyes covered by eyeshades and listen to music carefully selected by my therapists. I also may be asked to focus on selected photographs or objects or audiovisual presentations in order to help me gain insight into my pain, anxiety and/or fear of death.

I have been informed that any of the experimental LSD doses can produce a profound change in my mental state and that I may experience the psychological and physiological effects stated above. I may see and hear things that are not actually there, and/or other changes in my perceptions may occur. My sense of time may be altered (short lengths of time passing slowly or vice versa). I may experience very powerful pleasant or unpleasant emotions. I may have opposite feelings or thoughts at the same time. I may be extremely sensitive and aware of the environment, and may unrealistically judge how others feel about me. It may feel like my body and mind have separated. I may experience extreme changes of mood.

I understand that the effects of LSD are different for each experience by each person, that they usually begin within 20-40 minutes, that the peak effects are noted within 2-4 hours, and that most effects usually are gone within 8-12 hours.¹⁰⁶⁷

The amount of detail in this informed consent form will adequately prepare the subjects receiving either the 150 or the 400 microgram doses for a profound and powerful experience. The specific discussion of the time course of the effects along with the description of the remarkable emotional depths and shifts that can occur will provide sufficient clues for the subject receiving the 10 microgram dose to determine that the lowest dose has been administered. Members of the experimental team may not be able to determine whether subjects have received either the 150 or the 400 microgram dose, but they should be able to identify the subjects receiving the 10 microgram doses.

Dr. Evgeny Krupitsky's Ketamine-assisted Psychotherapy (KPT) Study in Heroin Addicts

Dr. Evgeny Krupitsky, St. Petersburg (Russia) Scientific Research Center for Addictions and Psychopharmacology, is currently conducting research designed to compare the efficacy of multiple sessions of ketamine-assisted psychotherapy (three high-dose sessions, spaced four weeks apart) in heroin addicts with that of a single session (one high-dose session, then two counselling sessions, each four weeks apart). Each group will contain forty subjects. No placebo is being used and all subjects and experimenters will

¹⁰⁶⁷Unpublished draft of Informed Consent Form, personal communication, Dr. Yensen, March 24, 2000.

know which treatment each subject is receiving. Thus, the issue is moot as to whether subjects in this study will be able to determine the treatment they will receive by clues contained in the informed consent form.

The relevant section from the consent form, used both in the current study and in Dr. Krupitsky's previous study in heroin addicts comparing low-dose to high-dose ketamine-assisted psychotherapy,¹⁰⁶⁸ is reproduced below. This informed consent form contains suggestions about the likelihood of specific psychological content that the subjects in this study may experience, and also mentions the link between those subjective experiences and the therapeutic potential of the ketamine session. This informed consent form is sufficiently detailed so that if the protocol design for the current study had included either an active or an inactive placebo, the subjects would almost certainly have been given enough information so that most or all could distinguish either an active or inactive placebo from either a low or a high dose of ketamine. Dr. Krupitsky's informed consent form states as follows:

Soon after the injection you will enter an unusual state of consciousness: you will be detached from the regular world around you and submerged to the deep levels of your subconsciousness which play an important role in your addiction. For about one hour you may experience the separation of consciousness from the body and the dissolving of the ego. In this state of consciousness you will experience very bright visions which have an important symbolic meaning. You may deeply feel the negative sides of addiction, the positive side of abstinence, the relief from heroin dependence and re-birthing for a new life. These visions may induce important insights concerning your personal problems, your system of values, notions of self and the world around you, and the meaning of your lives. All of these insights may entail positive changes in your personality, which will be important for the shift to a new lifestyle without heroin. The psychotherapist will supervise you during the session and his influences will help you a lot in your personal transformation (shift) to the heroin-free life.¹⁰⁶⁹

Dr. Krupitsky reported that his previous study comparing low-dose to high-dose ketamine-assisted psychotherapy was successful as a single-blind study, with the subjects unable to determine which dose of ketamine they had received. The reduced but still quite noticeable psychoactivity of the low dose aided the study to successfully implement a single

¹⁰⁶⁸Krupitsky E, Burakov A, Romanova T, Strassman R, Grinenko A. Ketamine-Assisted Psychotherapy (KPT) of Heroin Addiction: Immediate Effects and Six Months Follow-up. *Bull MAPS* 9 (1999) 4:21-26. <http://www.maps.org/news-letters/v09n4/09421kru.html>

¹⁰⁶⁹Informed Consent Form, translated into English by Dr. Krupitsky, March 12, 2000.

blind methodology. Dr. Krupitsky commented, “We have never asked subjects to guess which group they were in. As for the subjects, they have never had a ketamine experience before, so they were not able to determine which dose they received. Even with a low dose they were quite impressed by the procedure, so that it was not important for them to ask about the dose...It is probably correct that in most cases (however, not in 100%) subjects would have been able to distinguish ketamine (low or high dose) from inactive placebo, if we had included the use of an inactive placebo in the design.”¹⁰⁷⁰

Though the use of either a low dose or a high dose of ketamine did result in an effective single-blind study, the study as implemented failed as a double-blind study. The experimental team was able consistently to guess correctly which dose was administered to the subjects. Dr. Krupitsky attributed this success to the expertise in recognizing and working with the ketamine effect that the treatment team had built up over their more than 15 years of working with ketamine-assisted psychotherapy.^{1071 1072 1073} Dr. Krupitsky commented “I think that in about 90% of the cases or even more we were almost certain which dose had been injected. However, we have never been 100% sure about the dose.”¹⁰⁷⁴

The Failure to Blind and the Need for a Higher Standard Than Comparison to Placebo

The informed consent forms that subjects need to review and sign prior to participating in psychedelic psychotherapy research will unavoidably provide a substantial number of clues about how to recognize the subjective effects of the psychedelic drug being administered. By virtue of the uniquely powerful and dramatic effects of fully therapeutic doses of psychedelic drugs, subjects will almost invariably experience profound alterations in their cognitive and emotional processing. These subjective effects combined with the information provided in the informed consent forms will permit most if not all subjects to recognize whether they have received a fully therapeutic dose of the psychedelic drug being investigated or an inactive placebo, an active placebo or a threshold dose of the psychedelic drug.

As a result of the close interaction between the subjects and the therapeutic team, the

¹⁰⁷⁰personal communication, Dr. Krupitsky, March 10, 2000.

¹⁰⁷¹Krupitsky E, Grinenko A. Ketamine Psychedelic Therapy (KPT): A Review of the results of ten years of research. *J Psychoact Drug* 29 (1997) 2:165-183.

¹⁰⁷²Krupitsky E, Grinenko A, Karandashova G, Berkaliyev T, Moshkov K, Borodkin, Y. Metabolism of biogenic amines induced by alcoholism narcopsychotherapy with ketamine administration. *Biogenic Amines* 7 (1990): 577-582.

¹⁰⁷³Krupitsky E, Grinenko A, Berkaliyev T, Paley A, Petrov V, Moshkov K, Borodkin, Y. The combination of psychedelic and aversive approaches in alcoholism treatment: the affective contra-attribution method. *Alcohol Treat Q* 9 (1992): 99-105.

¹⁰⁷⁴personal communication, Dr. Krupitsky, March 10, 2000.

subjects' outwardly visible response to the powerful subjective effects of a full dose of the test drug will offer readily apparent clues to the experimental team as to whether a full dose of the psychedelic drug has been administered. Most if not all members of the experimental team will be able to determine whether the subjects have received either a full therapeutic dose of a psychedelic drug, an inactive placebo, an active placebo or a threshold dose of the psychedelic drug.

A double-blind may be achieved in limited instances. Subjects and members of the experimental teams will have some difficulty distinguishing between incrementally different doses of the psychedelic drug, such as between a low and a moderate dose or between a moderate and a high dose, or between active or inactive placebo and a low dose of the psychedelic. For example, Dr. Strassman noted, "In our DMT work, people regularly mistook the low dose for [inactive] placebo."¹⁰⁷⁵ However, these instances do not include the comparison of most importance in psychedelic psychotherapy research, between a fully therapeutic dose and either an active or an inactive placebo.

The practical failure to achieve a double-blind between psychedelic psychotherapy and inactive or active placebo legitimately introduces questions of experimental bias. This concern over experimental bias does justify the imposition of a higher standard of proof than FDA uses for the approval of other drugs in which the test drug is simply compared to placebo. A higher standard of proof than comparison of psychedelic psychotherapy to placebo is needed for the approval of psychedelic psychotherapy, even though previous sections of this chapter have determined that the use by FDA of a higher standard cannot be justified on the basis of the high-potential of abuse of psychedelics when used non-medically, on the impact of information about the possible medical uses of psychedelics on non-medical use patterns, or on ethical considerations.

What this higher standard should be, as well as what protocol design measures should be adopted to address the failure of the double-blind, are the subject of the remainder of this chapter.

Methods to Reduce Bias when the Double-Blind Fails

When the double-blind fails, both the subject and the experimenter may let bias affect all outcome measurements and ratings. As Dr. Temple explained, "Inability to blind and potential bias makes any subjective endpoint less credible... (this is not to say that subjective end-points are not of value)."¹⁰⁷⁶ One response to this increased potential for bias is the use of solid, objective outcome measures. Unfortunately, solid, objective

¹⁰⁷⁵personal communication, Dr. Strassman, April 4, 2000. Dr. Strassman noted that even though subjects often mistook the low dose for the placebo, the 100-item self-report questionnaires that they filled out rating their experience, the Hallucinogen Rating Scale (HRS), "was more sensitive to estimating dose effects than a global/gestalt 'guess' on the part of the volunteer."

¹⁰⁷⁶Temple R. NIH Workshop on the Medical Utility of Marijuana, Slide 24, "Appetite, Cachexia, Wasting."

outcome measures are more common in studies into the treatment of externally observed phenomena, such as physical illnesses, but are more difficult to obtain when the phenomena under study are changes in the patients' subjective mood states, the likely focus of psychedelic psychotherapy research. One possibility is to supplement subjective data generated through questionnaires that rely on patient self-reports with measures of function and behavior that can be observed and measured by outside raters such as significant others, employers, etc. Quality of life measures, though usually based primarily on patient self-reports, can also incorporate data from outside evaluators.¹⁰⁷⁷ ¹⁰⁷⁸ In studies testing psychedelics in the treatment of substance abuse, measures of drugs or alcohol use such as urine tests and other drug use screens can serve quite well as objective outcome measures.

Another necessary step towards reducing bias when double-blind methodology fails is the use of independent raters, a practice that is relatively easy and inexpensive to implement.¹⁰⁷⁹ The use of blind raters can eliminate bias that stems from evaluators who are aware of the treatment conditions to which the patients being evaluated have been exposed. When evaluators are aware of which treatment the subjects have received, they may be motivated consciously or unconsciously to bias the outcome ratings measuring the effects of the interventions.¹⁰⁸⁰ With the assessment of outcomes taken out of the hands of any members of the experimental team who may know which patients have received which substances, the validity of the outcome measures is strengthened.

What is Lost when the Double-Blind Fails?

Each study must be individually analyzed to see what sorts of bias or other problems may be encountered when the double-blind fails. For example, when subjects know they are in the placebo group, they may see little point in remaining in a study. Subjects in the placebo group may drop out of the study at a higher rate than subjects receiving the test drug, compromising subject retention and possibly biasing results. If placebo subjects do remain in the study, patient management may suffer as a result of a possibly lower motivation to participate in all follow-up activities. Subjects in the placebo group might also seek out other treatments at a higher rate than subjects receiving the test drug, confounding

¹⁰⁷⁷Byock I, Merriman M. Measuring quality of life for patients with terminal illness: the Missoula-VITAS quality of life index. *Palliat Med* 12 (Jul 1999) 4:231-44.

¹⁰⁷⁸Anderson R. What does it Mean? Anchoring Psychosocial Quality of Life Score Changes with Reference to Concurrent Changes in Reported Symptom Distress. *Drug Info J* 33 (1999) 2:445-453.

¹⁰⁷⁹Guy W, Gross M, Dennis H. An alternative to the double-blind procedure. *Am J Psychiat* 123 (1967): 1505-1511.

¹⁰⁸⁰ICH Draft Consensus Guideline, Choice of Control Group in Clinical Trials, Section 2.1.2 Ability to Minimize Bias states, "The placebo-controlled trial, using randomization and blinding, generally reduces subject and investigator bias maximally, but such trials are not impervious to blind-breaking through recognition of pharmacologic effects of one treatment (perhaps a greater concern in cross-over designs); blinded outcome assessment can enhance bias reduction in such cases."

their outcome measures with unreported interventions not accounted for in the data analysis.

As an illustrative example, the consequences of the failure of the double-blind in Dr. Pahnke's Good Friday experiment will be examined. There were no resulting problems with subject retention or patient management during the experimental phase of the study because there was only one experimental session. Though there is no evidence to suggest that there was bias in the self-reported outcome measures, this cannot be ruled out. Some subjects who knew they received the psilocybin might have exaggerated their evaluations of their experiences in order to please the experimental team, impress their fellow subjects, or convince themselves that their experience was more profound than it actually was. Some subjects in the control group could perhaps have minimized their self-reported ratings of their subjective experience since they may also have wanted to provide evidence supportive of the hypothesis of the experimental team. Alternatively, some subjects in the control group could have exaggerated their self-reported ratings of their experience to demonstrate that they did not need drugs to achieve a mystical experience.

Estimating the magnitude of any bias, if bias was indeed a factor, is a matter of guesswork. Due to the profound nature of the psilocybin experience, it is most likely the case that the magnitude of any bias that did occur was less than the magnitude of the self-reports of the direct effects of the psilocybin. The possibility of some degree of bias in the self-reported outcome measures does not fundamentally invalidate Dr. Pahnke's observation that, "eight out of ten of the experimental subjects experienced at least seven out of the nine categories [dimensions of mystical experience]...there was one control subject who scored fairly high on sacredness and sense of peace and that he himself, in his written account, said "It was a very meaningful experience, but in the past I've certainly had one that was much more so." ¹⁰⁸¹ Dr. Pahnke's conclusion holds that "the persons who received psilocybin experienced to a greater extent than did the controls the phenomena described by our typology of mysticism." ¹⁰⁸² The loss of the double-blind does suggest that restraint should be used in attributing the experiences of the subjects exclusively to the psilocybin, with non-pharmacological factors playing a major role, as Dr. Pahnke himself acknowledged. ¹⁰⁸³

Dr. Pahnke's study also included a six-month follow-up evaluation in which the subjects rated the impact of the experience on their lives. The loss of the double-blind did not compromise subject retention, since all subjects participated in the six-month follow-up. All but two psilocybin subjects reported their experience to have resulted in persisting positive benefits. While bias could still operate at the six-month follow-up, the

¹⁰⁸¹Pahnke W. The contribution of the psychology of religion to the therapeutic use of psychedelic substances. in Abramson H. (ed.) *The use of LSD in psychotherapy and alcoholism*. New York: Bobbs-Merrill, 1967: 648.

¹⁰⁸²Pahnke (1963): 220.

¹⁰⁸³Pahnke W. Drugs and Mysticism. in (ed.) Aaronson B, Hoffer A. *Psychedelics- The Uses and Implications of Hallucinogenic Drugs*. Garden City, NY: Anchor Books, 1970: 145-165.

psychological pressures that might have influenced subjects to report persisting positive benefits would probably have lessened by the six-month follow-up. The persistence of bias due to these psychological pressures would have been even less likely at the twenty-five year follow-up, when all the psilocybin subjects who were willing to be interviewed reaffirmed the essential validity and long-lasting impact of their psilocybin-assisted spiritual experience.¹⁰⁸⁴

In Dr. Pahnke's experiment, the failure of the double-blind probably had a relatively small impact on the results and was mitigated by other aspects of the study design such as the use of matched controls, random assignment to placebo or test drug, the surprise use of an active placebo condition that prolonged the double-blind for as long as possible, an unusually detailed questionnaire designed specifically for the study to evaluate the characteristics of the subjective experiences reported by the subjects, and the intentional absence of any prior discussion with the subjects of the typology of mystical experiences that would be assessed by the questionnaire. When the double-blind methodology fails, the other methodological details of the study need to be carefully and rigorously designed.

Overreliance on the Double-Blind Methodology

Even when the goal of research is simply to determine the pharmacological effects of a non-psychoactive chemical compound independent of set and setting, strong attacks have been made on the overreliance on the double-blind methodology as the only method of generating valid results. According to Dr. Louis Lasagna, Director of the Center for the Study of Drug Development at Tufts University, valuable information can be generated without the use of the double-blind methodology. Dr. Lasagna was one of the pioneers in the adoption of the double-blind methodology in clinical research,¹⁰⁸⁵ yet writes:

We have witnessed the ascendancy of the randomized, double-blind, controlled clinical trial (RCCT), to the point where many in positions of authority now believe that data obtained via this technique should constitute the only basis for registering a drug or indeed for coming to any conclusions about its efficacy at any time in the drug's career. My thesis is that this viewpoint is untenable, needlessly rigid, unrealistic, and at times unethical... Modern trial techniques [were not] necessary to recognize the therapeutic potential of chloral hydrate, the barbiturates, ether, nitrous oxide, chloroform, curare, aspirin, quinine, insulin, thyroid, epinephrine, local anesthetics, belladonna, antacids, sulfonamides, and penicillin, to give a partial list.¹⁰⁸⁶

¹⁰⁸⁴Doblin (1991).

¹⁰⁸⁵Lasagna L. The Controlled Clinical Trial. Theory and Practice. *J Chronic Dis* 1 (1955): 353-367.

¹⁰⁸⁶Lasagna (1985):48.

Commenting about the attempt to remove the experimenter from the experiment completely, Drs. Tooley and Pratt remark:

In certain participant-observer situations (e.g. psychotherapy, education, change induction, action research) the purpose might be to influence the system under investigation as much as possible, but still accounting for (though now exploiting) the variance within the system attributable to the several significant and relevant aspects of the investigator's participant observation... From this perspective, the quixotic attempt to eliminate the effects of participant-observation in the name of a misplaced pseudo-objectivity is fruitless, not so much because it is impossible but because it is unproductive... From our point of view... the question becomes not how to eliminate bias (unaccounted-for influence) of participant observation, but how optimally to account for and exploit the effects of the participant observation transaction in terms of the purposes of the research.¹⁰⁸⁷

Dr. Hoffer goes further and suggests that while the double-blind methodology is frequently ineffective in its stated aim of producing a double-blind, it is not just unproductive but counter-productive when applied to a psychotherapeutic context. He notes:

There are at least three major variables in any therapeutic program. The first is the feeling of trust or faith the patient has in his doctor and, therefore, in his therapy. The second factor is the faith or confidence the physician has in himself and in the line of therapy he proposes to use. The third is the therapy. The best results are obtained when all three variables are set at their optimum level... The double-blind technique makes it difficult to sustain these [first] two variables at their optimum level.¹⁰⁸⁸

Pharmacological and Non-Pharmacological Variables

Dr. Hoffer, and Drs. Tooley and Pratt point out that a valid approach to psychotherapy research is to seek to maximize the combined effect of the particular therapeutic approach with the unique contribution made by the therapist participating with full awareness as to the therapy that is being delivered. The practical difficulties in conducting successful double-blind studies comparing full doses of psychedelics to inactive or active placebos complicate the ability to design a study to separate out the role of the pharmacological from the non-pharmacological variables. Yet rather than try to separate

¹⁰⁸⁷Tooley, Pratt. Letter to the editor. *Behav Sci* 9 (1964) 3:254-56.

¹⁰⁸⁸Hoffer (1967): 126.

these factors out, another approach is to maximize the therapeutic effect of the combination while seeking methods other than the double-blind study to evaluate outcomes and compare the effects of psychedelic psychotherapy with alternative treatments.

Psychedelic psychotherapy, similar in kind if not in degree to other forms of psychiatric interventions involving the administration of pharmacological medications, consists of a combination of pharmacological and non-pharmacological interventions. With psychedelic psychotherapy, the non-pharmacological variables that stem from the psychological state of the patient, including preparation for the psychedelic experience and the expectations for that experience, have been called the “set, ” while the non-pharmacological variables that stem from the context in which the drugs are administered, including the physical environment and the theoretical orientation and attitudes of the therapeutic team, have been called the “setting.”¹⁰⁸⁹ Due to the profound nature of an acute psychedelic experience, the set and setting variables exert a powerful influence over the course of the subjective experience. The set and setting variables influence the ability of subjects to experience fully the internal changes that can be elicited by psychedelics, to interpret the experiences in meaningful ways, to integrate the experiences over time, and most importantly, to generate and sustain therapeutic outcomes. Dr. Carl Salzman, an early psychedelic researcher and currently a Professor of Psychiatry at Harvard Medical School, explains, “In many ways, the effects of the psychedelic substances are unique and particularly sensitive to non-drug factors that may surround the experience.”¹⁰⁹⁰

The classic psychotropic medications that have been developed by the pharmaceutical industry and marketed as prescription drugs for a variety of psychiatric indications, such as Prozac for mild to moderate depression, lithium for major depression and thiorazine for psychosis, depend to a lesser extent than the psychedelics on non-pharmacological variables. Their mechanisms of action are almost exclusively seen in terms of their pharmacological effects, primarily on the levels of various neurotransmitters such as serotonin. They are administered on a take-home basis and are consumed on a daily basis with only intermittent psychiatric supervision evaluating the chronic but not the acute effects of the medications. Nevertheless, studies have suggested that even with anti-psychotic pharmaceutical medications, the combination of medication with non-pharmacological interventions such as social therapies can work better than either medication alone or psychotherapy alone.¹⁰⁹¹

With each form of psychedelic therapy, the combination of the psychedelic drug as

¹⁰⁸⁹Zinberg N. *Drug, set and setting*. New Haven: Yale University Press, 1984.

¹⁰⁹⁰Salzman C. Controlled Research with Psychedelic Drugs. in (eds.) Hicks R, Fink P. *Psychedelic Drugs- Proceedings of a Hahnemann Medical College and Hospital Symposium, November 22-24, 1968*, New York: Grune and Stratton, 1969: 26.

¹⁰⁹¹Karon B. Psychotherapy versus Medication for Schizophrenia: Empirical Comparisons. in (eds.) Fisher S, Greenberg R. *The Limits of Biological Treatments for Psychological Distress- Comparisons with Psychotherapy and Placebo*. Hillsdale, New Jersey: Lawrence Erlbaum Associates, 1989: 105-150.

catalyst and the technique of therapy contributes to the subjects' reported experiences and clinical outcomes. Psychedelic psychotherapy is an inextricable combination of pharmacological and non-pharmacological variables, calling into question the goal of conducting double-blind studies to isolate out the solitary contribution of the drug. The piercing of the double-blind makes it impossible to eliminate all bias and to determine with precision the relative contributions of the psychedelic drug and the particular therapeutic approach that accompanied and provided the context for the psychedelic experience.

The prior expectations of the therapist and the patient about the efficacy of the psychedelic drug would contribute to the outcomes of the group receiving the psychedelic drug in combination with psychotherapy, but would not be a factor in the group receiving the psychotherapy-only treatment. Even determining the efficacy of psychotherapy alone or conventional psychiatric medication alone is complicated as a result of factors other than the psychotherapeutic technique or psychiatric drug.¹⁰⁹² Drs. Hollon, Sheldon and Loosen have proposed that any adequate study of a specific method of psychotherapy would need to evaluate independently the “non-specific factors associated with the therapeutic relationship and the theoretically specified component of psychotherapy, that acts over and above the component of change contributed by processes unrelated to treatment.”¹⁰⁹³ For a complete dissection of the independent contributions of a single method of psychotherapy, a single pharmacotherapy, and the combination of the two, they have proposed a nine-factorial design. The added conditions are due to the separation of the effects of both the psychotherapy and the pharmacotherapy into two discrete components, specific and non-specific. The psychotherapy conditions they called attention-placebo (non-specific) and clinically representative psychotherapy (specific). The pharmacotherapy conditions were called attention-placebo (non-specific) and clinically representative pharmacotherapy (specific). A no-treatment control was also added. The authors state, “We do not necessarily recommend such a design; it seems to us to be so cumbersome and unwieldy as to be impractical.”¹⁰⁹⁴

If psychedelic psychotherapy studies were designed specifically to measure only the pure drug effects, the failure of the double-blind would be irreparably damaging to the struggle to generate any experimentally-determined conclusions. However, if the goal of the research is to foster therapeutic change through the use of psychedelic-assisted psychotherapy, which combines pharmacotherapy and a specific form of psychotherapy, the loss of the double-blind is of lesser significance. Each experiment can be considered to

¹⁰⁹² For a thorough discussion of non-specific factors in drug therapy, see Rickels K. (ed.) *Non-Specific Factors in Drug Therapy*. Springfield, Illinois: Charles C. Thomas Publishers, 1968.

¹⁰⁹³ Hollon S, Shelton R, Loosen P. Research Considerations in Evaluating Combined Treatment. in (eds.) Beitman B, Klerman G. *Integrating Pharmacotherapy and Psychotherapy*. Washington, D.C.: American Psychiatric Press, 1991: 364-365.

¹⁰⁹⁴ *Ibid.*, 372.

be explicitly designed to maximize the combined effect of psychedelics as used within a specific form of therapy. The research challenge shifts from trying to precisely isolate the impact of the drug itself from that of the therapy to determining the relative efficacy of the combined treatment as compared to that therapy without the psychedelic, as well as to other alternative treatments.

Standard of Proof for Psychedelic Psychotherapy When Double-Blind Fails

The challenge to this point has been to determine an appropriate standard of proof to use in the evaluation of psychedelic psychotherapy, taking into account the inability to conduct an effective double-blind experiment comparing psychedelics to placebos. The critical point to recognize is that even though it is too difficult to separate out with precision the independent contributions made by all the specific and non-specific pharmacological and non-pharmacological factors involved in psychedelic psychotherapy, it is nevertheless possible to compare the efficacy of psychedelic psychotherapy with a psychotherapy-only condition that includes all the same psychotherapeutic elements as the psychedelic psychotherapy treatment but not the psychedelic drug. While this comparison will not be double-blind, it is an appropriately higher standard than the comparison of psychedelic psychotherapy to a placebo treatment that includes neither active drug nor psychotherapy that also will not remain blinded.

A similar approach in the study of medications to treat cocaine addiction has been recommended by Dr. Edward Nunes. He observed, “An argument can be made that medication trials should be superimposed on a strong psychosocial intervention, so that the trial is informative in terms of what medication has to add to good standard treatment. Anything less may lack clinical credibility with the control group becoming a ‘straw man’ receiving poor care.”¹⁰⁹⁵

There is also an important ethical advantage in using as a standard of proof the comparison of psychedelic psychotherapy to psychotherapy only, due to the fact that the psychotherapy-only condition is an active treatment with some therapeutic elements. For example, in research conducted into the use of LSD in the treatment of alcoholism in the late 1960s and early 1970s under the direction of Dr. Albert Kurland, “The preparation for the drug session involves an average of about twenty hours of intensive psychotherapy.”¹⁰⁹⁶ Additional hours of therapist contact take place during the experimental session and during the post-session integrative psychotherapy. As a result of the control condition not being a placebo condition but being a psychotherapy-only condition with some therapeutic elements,

¹⁰⁹⁵Nunes E. Methodologic Recommendations for Cocaine Abuse Clinical Trials: A Clinician-Researcher’s Perspective. in (eds.) Tai B, Chiang N, Bridge P. *Medication Development for the Treatment of Cocaine Dependence: Issues in Clinical Efficacy Trials*. NIDA Research Monograph 175. Washington, DC, NIH Publication 97-4125, 1997: 80.

¹⁰⁹⁶Kurland A, Savage C, Pahnke W, Grof S, Olsson J. LSD in the Treatment of Alcoholics. *Pharmakopsychiatrie Neuro-Psychopharmacologie*4 (1971) 2:84.

the ethical problems associated with randomizing patients in need of treatment to a placebo group are addressed to the extent that the psychotherapy-only condition is actually therapeutic. This ethical advantage is present in those instances where there are no accepted treatments, either drug or non-drug, as well as where there are accepted treatments.

LSD in the Treatment of Alcoholics: Need for Psychotherapy-Only Condition

Arguments about the necessity of using a psychotherapy-only control group to evaluate claims of efficacy from psychedelic psychotherapy lie at the core of the heated debate over whether or not LSD was demonstrated to be effective in the treatment of alcoholism. In what is considered the most influential critique of the use of LSD-assisted psychotherapy in the treatment of alcoholics,¹⁰⁹⁷ Drs. Ludwig, Levin and Stark evaluated one of the largest and most important studies in the LSD/alcoholism treatment literature, conducted under the direction of Dr. Kurland at the Maryland Psychiatric Research Center at Spring Grove State Hospital. The study involved 135 patients who received either one therapeutic session with 50 micrograms of LSD (low dose) or with 450 micrograms (high dose).¹⁰⁹⁸ ¹⁰⁹⁹ An unequal randomization was employed, with twice as many subjects allocated to the high-dose group as compared to the low-dose group. The results of the study were that 53% of the high dose group but only 33% of the low dose were considered rehabilitated at the six-month follow-up, a significant difference.¹¹⁰⁰ At the twelve month and eighteen month follow-ups, the rates of rehabilitation for the two groups were no longer significantly different from each other. However, the “overall level of improvement was considerably better for both groups than usual improvement for other alcoholics in the same

¹⁰⁹⁷Ludwig A, Levine, J. Stark L. *LSD and Alcoholism- A Controlled Study of Treatment Efficacy*. Springfield, IL.: Charles Thomas, 1970.

¹⁰⁹⁸Kurland (1971).

¹⁰⁹⁹For additional studies on psychedelics in the treatment of alcoholism, see Sarett M, Cheek F, Osmond H. Reports of wives of alcoholics of effects of LSD-25 treatment of their husbands. *Arch Gen Psychiat* 14 (Feb 1966) 2:171-8; Kurland A, Unger S, Shaffer J, Savage C. Psychedelic therapy utilizing LSD in the treatment of the alcoholic patient: a preliminary report. *Am J Psychiat* 123 (Apr 1967) 10:1202-9; Pahnke W, Kurland A, Unger S, Savage C, Grof S. The experimental use of psychedelic (LSD) psychotherapy. *JAMA* 212 (Jun 1970) 11:1856-63; Hoffer A. Treatment of Alcoholism with Psychedelic Therapy. in (ed.) Aaronson B, Hoffer A. *Psychedelics- The Uses and Implications of Hallucinogenic Drugs*. Garden City, NY: Anchor Books, 1970: 357-365. Grof S, Soskin R, Richards W, Kurland A. DPT as an adjunct in psychotherapy of alcoholics. *Int Pharmacopsychiat* 8 (1973) 1:104-15.

¹¹⁰⁰Kurland (1971): 89. According to the study, “The follow-up ratings of adjustment were made by an independent team of social workers. Ratings were made on each patient on a predetermined 0-10 behavior rating scale. The Global Adjustment rating included occupational, interpersonal, and residential factors as well as the patient’s use of alcohol, with a score of zero indicating poorest adjustment and ten indicating superior adjustment. Zero in the scale measuring Drinking Behavior indicated daily alcohol consumption, and ten indicated total abstinence.”

setting without LSD-assisted psychotherapy.”¹¹⁰¹

In reviewing the data from his own studies of the use of LSD in the treatment of alcoholism, Dr. Ludwig argued, “It seems reasonable to conclude that, despite the enthusiasm that has been whipped up over LSD effects on alcoholism, the effectiveness of this form of therapy turns out to be a mirage.”¹¹⁰² Drs. Pahnke et al. looked at their data and expressed a different view, namely that, “a given alcoholic 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 six months later.”¹¹⁰³

In terms of methodology, Drs. Ludwig, Levin and Stark commented:

We do not believe that the sole use of a low-dose control condition employed was adequate to evaluate the effects of psychedelic therapy. If a control group were used in which patients received the same intensive preparation but received an active placebo or no drug at all, it would be possible to evaluate the contribution of the high LSD dosage to the total treatment impact. Moreover, if another control condition were employed whereby the high LSD dosage would be administered to patients who had received only *minimal* preparation, it would be possible to determine whether all the intensive preparation of patients and intensive therapist involvement were necessary in the first place in terms of good treatment outcome results.¹¹⁰⁴

Drs. Ludwig, Levin and Stark correctly point out that two additional control groups, one receiving high-dose LSD without intensive preparation and therapist involvement, and one receiving intensive preparation and similar psychotherapy without LSD, would have been helpful in enabling the researchers to start trying to isolate out the relative contributions of the non-pharmacological variables involved in the psychotherapeutic interventions from the pharmacologically-mediated effects of LSD. However, from a practical point of view in light of resource constraints, the approach the Kurland team adopted made sense. They sought first to determine whether there was any efficacy with the use of a specific form of

¹¹⁰¹Yensen R, Dryer D. Thirty Years of LSD Research: The Spring Grove Experiment and its Sequels. in (eds.). Schlichting M, Leuner H. *Worlds of Consciousness. Vol 5 Abstracts and Selected Papers from the 1st International Congress of the European College for the Study of Consciousness (ECSC), Gottingen, Germany, September 24-27. 1992.* Berlin: Verlag fur Wissenschaft und Bildung, 1995: 169.

¹¹⁰²Ludwig A. LSD Treatment in Alcoholism, in (ed.) Gamage J, Zerkin E. *Hallucinogenic Drug Research: Impact on Science and Society.* Proceedings of the First Annual Symposium of the Student Association for the Study of Hallucinogens. Beloit, Wisconsin, 1970: 47.

¹¹⁰³Pahnke et al. (1970): 1857.

¹¹⁰⁴Ludwig, Levine, Stark (1970): 237.

LSD-assisted psychotherapy in the treatment of alcoholics before conducting more refined studies seeking to determine the relative contributions of the different elements of the treatment package. Furthermore, the demonstration of a significant treatment effect from a specific form of LSD-assisted psychotherapy in a particular patient population in “adequate and well-controlled investigations” should be sufficient to obtain regulatory approval for that form of LSD psychotherapy. Refining the treatment could take place in the context of subsequent studies conducted after the treatment has been approved for prescription use.¹¹⁰⁵ Where the critique of Drs. Ludwig, Levin and Stark strikes home is the claim that the efficacy of the treatment could not be comprehensively evaluated without a control group receiving psychotherapy but no LSD, hence no “adequate and well-controlled investigations” had yet taken place.

Another methodological critique made by Drs. Ludwig, Levin and Stark was that Dr. Kurland’s team should have included a group that received a high dose of LSD without intensive preparation and attentive psychotherapy during the acute period of the effects of LSD. However, this critique raises serious ethical questions. Dr. Kurland and his team clearly believed that the intensive preparations and therapist involvement during the session helped to reduce the likelihood of serious adverse events and also increased the chances of beneficial therapeutic outcomes. For them to administer LSD to alcoholics without taking the necessary precautions to ensure safety and promote efficacy would be unethical. Furthermore, from the point of view of evaluating the safety and efficacy of LSD psychotherapy in the treatment of alcoholics, the central issues are not whether LSD administered with therapy is as safe and effective as LSD administered without therapy. The issues are how the safety and efficacy of therapy administered with LSD compares to therapy administered without LSD. The suggestion by Drs. Ludwig, Levin and Stark that Dr. Kurland’s team should have administered LSD to a group of alcoholics without therapy can be rejected. The suggestion by Drs. Ludwig, Levin and Stark that therapy without LSD be compared to therapy with LSD should be accepted wholeheartedly.

Drs. Ludwig, Levin and Stark considered the Kurland team’s comparison with the “usual improvement for other alcoholics in the same setting without LSD-assisted psychotherapy” to be inadequate, since the other alcoholics did not receive the same intensive preparation and psychotherapy as did those receiving the LSD therapy, either low dose or high dose. Dr. Kurland and associates recognized the weakness of using historical controls and noted, “the psychedelic psychotherapy was successful in helping over half of the alcoholics treated in the program as opposed to a 12% improvement rate at 18 months follow-up for comparable alcoholics in the treatment facility at Spring Grove State Hospital.

¹¹⁰⁵From the point of view of a sponsor trying to market LSD, the financial incentive for conducting controlled follow-up studies is reduced once the LSD is approved for marketing. From a scientific perspective, however, the incentive for understanding the therapeutic contributions of various elements of a treatment package is fundamentally increased after it has been determined that the treatment is, in fact, efficacious.

This 12% factor is from a prior study and does not represent a concomitant comparison control group.”¹¹⁰⁶ Furthermore, Drs. Kurland and associates acknowledged that the inclusion of a psychotherapy-only control group would have strengthened their study. They stated, “In retrospect, a control group receiving no LSD would have been helpful in differentiating the exact role of psychotherapy as opposed to LSD session. In actual practice, however, these two factors, it must be pointed out, are closely interwoven and work together as a unified treatment approach.”¹¹⁰⁷

As noted by Drs. Kurland and associates and by Drs. Ludwig, Levin and Stark, the addition of a psychotherapy-only treatment group to which patients could be randomly assigned would remove the uncertainty about whether the use of either a low-dose or high-dose of a psychedelic significantly improves the efficacy of the psychotherapeutic treatment. For the purposes of designing an “adequate and well-controlled investigation” of psychedelic psychotherapy, the statements of Drs. Kurland and associates and Drs. Ludwig, Levin and Stark lend further support to the proposal that the essential standard of proof used to evaluate psychedelic psychotherapy should be a comparison of a group receiving psychedelic psychotherapy against a psychotherapy-only control group.

NIMH Treatment of Depression Collaborative Research Program

Valuable insights for the choice of research methodologies that can be most effective in evaluating psychedelic psychotherapy can be found in the National Institute of Mental Health’s Treatment of Depression Collaborative Research Program.¹¹⁰⁸ The NIMH study, for which planning began in 1984, involved extensive preparation and evaluation of the most appropriate methodologies for comparing interpersonal psychotherapy, cognitive behavior therapy, pharmacotherapy (imipramine) with clinical management, and placebo with clinical management.^{1109 1110 1111 1112 1113} The clinical management (CM) component

¹¹⁰⁶Kurland et al. (1971): 92.

¹¹⁰⁷Ibid.,92.

¹¹⁰⁸Elkin I, Shea M, Watkins J, Imber S, Sotsky S, Collins J, Glass D, Pilkonis P, Leber W, Docherty J, et al. National Institute of Mental Health Treatment of Depression Collaborative Research Program. General effectiveness of treatments. *Arch Gen Psychiat* 46 (Nov 1989) 11:971-82; discussion 983.

¹¹⁰⁹Elkin I, Parloff M, Hadley S, Autry J. NIMH Treatment of Depression Collaborative Research Program. Background and research plan. *Arch Gen Psychiat* 42 (Mar 1985) 3:305-16.

¹¹¹⁰Imber S, Glanz L, Elkin I, Sotsky S, Boyer J, Leber W. Ethical issues in psychotherapy research. Problems in a collaborative clinical trials study. *Am Psychol* 41 (Feb 1986) 2:137-46.

¹¹¹¹Rounsaville B, Chevron E, Prusoff B, Elkin I, Imber S, Sotsky S, Watkins J. The relation between specific and general dimensions of the psychotherapy process in interpersonal psychotherapy of depression. *J Consult Clin Psychol* 55 (Jun 1987) 3:379-84.

¹¹¹²Elkin I, Pilkonis PA, Docherty JP, Sotsky SM Conceptual and methodological issues in comparative studies of psychotherapy and pharmacotherapy, I: Active ingredients and mechanisms of change. *Am J*

was described as providing “guidelines, not only for the management of medications and side effects and review of the patient’s clinical status, but also for providing the patient with support and encouragement and direct advice if necessary. Although specific psychotherapeutic interventions were proscribed (especially those that might overlap with the two psychotherapies), the CM component approximated a ‘minimally supportive therapy’ condition.”¹¹¹⁴

The NIMH study was a complex, multi-site investigation involving 250 “nonbipolar, nonpsychotic depressed outpatients” randomized into one of four treatment conditions, each lasting sixteen weeks and delivered by a total of 28 therapists at three treatment sites.¹¹¹⁵ It remains to date the most comprehensive and rigorous comparative examination ever conducted between different forms of psychotherapy and pharmacotherapy, with the data generated subjected to continued fruitful analyses over the years.

From a methodological point of view, the NIMH study demonstrated that particular forms of psychotherapy could be standardized. This significant finding indicates that psychedelic psychotherapy can also be standardized and studied, in both the form that includes the psychedelic drug and the form that includes only the psychotherapeutic components without the administration of the psychedelic drug. In the NIMH study, standardization was achieved through the use of “a detailed manual describing the theoretical underpinning of the approach, the general strategies involved, the major techniques that could be used, and suggestions for dealing with specific problems. During the training/pilot phase of this study, the therapists all received further training in their respective approaches, met competence criteria in carrying out the treatments as described in the protocol, and were monitored throughout the outcome study.”^{1116 1117 1118 1119}

Dr. Daniel X. Freedman states that in the NIMH study, “standardization of the

Psychiat 145 (Aug 1988) 8:909-17.

¹¹¹³Elkin I, Pilkonis P, Docherty J, Sotsky S. Conceptual and methodological issues in comparative studies of psychotherapy and pharmacotherapy, II: Nature and timing of treatment effects. *Am J Psychiat* 145 (Sep 1988) 9:1070-6.

¹¹¹⁴Elkin et al. (1989): 973.

¹¹¹⁵*Ibid.*, 971-2.

¹¹¹⁶*Ibid.*, 972.

¹¹¹⁷Fawcett J, Epstein P, Fiester S, Elkin I, Autry J. Clinical management--imipramine/placebo administration manual. NIMH Treatment of Depression Collaborative Research Program. *Psychopharmacol Bull* 23 (1987) 2:309-24.

¹¹¹⁸Beck A, Rush A, Shaw B, Emery G. *Cognitive Therapy of Depression*. New York, NY: Guilford Press, 1979.

¹¹¹⁹Klerman G, Weissman M, Rounsaville B, Chevron E. *Interpersonal Psychotherapy of Depression*. New York, NY: Basic Books, 1984.

two brief psychotherapies was achieved. For the general goal of systematic psychotherapy research, this is an important finding.”^{1120 1121} According to Dr. C Hill, “therapists exhibited more behaviors appropriate to their own respective treatment approaches than to other treatment approaches.¹¹²² Subsequent studies in other patient populations comparing psychotherapy with pharmacotherapy have also successfully standardized the delivery of psychotherapy within an experimental context.^{1123 1124} Other research groups have also developed manuals for specific forms of psychotherapy,¹¹²⁵ and demonstrated that independent judges can successfully determine whether therapists provide treatment consistent with the techniques described in the manuals.^{1126 1127}

The NIMH study also demonstrated that psychotherapy can be compared to pharmacotherapy within an experimental design in which patients and therapists are aware of which patients are receiving the psychotherapy. In the NIMH study, there was a double-

¹¹²⁰Freedman D. Editorial Note. *Arch Gen Psychiat* 46 (1989 Nov) 11:983.

¹¹²¹For Dr. Freedman’s view of LSD research, see Freedman D. Problems and Prospects of Research with the Hallucinogens. in(ed.) Gamage J and Zerkin E. *Hallucinogenic Drug Research: Impact on Science and Society*. Proceedings of the First Annual Symposium of the Student Association for the Study of Hallucinogens. Beloit, Wisconsin, 1970: 1-10.

¹¹²²Hill C, O’Grady K, Elkin I. Applying the Collaborative Study Psychotherapy Rating Scale to rate therapist adherence in cognitive-behavior therapy, interpersonal therapy, and clinical management. *J Consult Clin Psychol* 60 (Feb 1992) 1:73.

¹¹²³Carroll K, Rounsaville B, Gordon L, Nich C, Jatlow P, Bisighini R, Gawin F. Psychotherapy and pharmacotherapy for ambulatory cocaine abusers. *Arch Gen Psychiat* 51 (Mar 1994) 3:177-87. According to the authors, “We conducted the first randomized clinical trial evaluating psychotherapy and pharmacotherapy, alone and in combination, as treatment for ambulatory cocaine abusers... All treatments were manual-guided, delivered by experienced therapists, and monitored to promote the integrity of both forms of treatment.”

¹¹²⁴Jarrett R, Schaffer M, McIntire D, Witt-Browder A, Kraft D, Risser R. Treatment of atypical depression with cognitive therapy or phenelzine:a double-blind, placebo-controlled trial. *Arch Gen Psychiat* 56 (May 1999) 5:431-7. The double-blind in this study was between phenelzine and placebo, not between phenelzine and cognitive therapy.

¹¹²⁵Luborsky L, DeRubeis R. The Use of Psychotherapy Treatment Manuals: A Small Revolution in Psychotherapy Research Style. *Clin Psychol Rev*4 (1985): 5-10.

¹¹²⁶Luborsky L, Woody G, McLellan T, O’Brien C. Can Independent Judges Recognize Different Psychotherapies? An Experience with Manual-Guided Therapies. *J Consul Clin Psychol* 50 (1982) 1:49-62. Three different treatments for drug abusers were tested; drug counseling, supportive-expressive psychotherapy, and cognitive-behavioral. Judges were able to identify correctly which therapy was being administered 70% of the time in Study 1, and 80% of the time in Study 2.

¹¹²⁷DeRubeis R, Hollon S, Evans M. Can Psychotherapies for Depression be Discriminated? A Systematic Investigation of Cognitive Therapy and Interpersonal Therapy. *J Consult Clin Psychol* 50 (1982): 49-62.

blind pharmacology treatment with either active medication or inactive placebo. However, no attempt was made to blind the psychotherapy condition, given the inherent difficulties in conducting a double-blind study with psychotherapy as one treatment condition.

The NIMH study evaluated a non-pharmacological variable known as the therapeutic alliance, a measure of the strength of the relationship between patient and therapist. The therapeutic alliance was found to have a significant effect on clinical outcome for both psychotherapies and for active and placebo pharmacotherapy.¹¹²⁸ Other characteristics of effective therapists were also identified in a subsequent data analysis.¹¹²⁹ Of relevance to the choice of patient population for psychedelic psychotherapy, the NIMH study demonstrated the importance of matching patients to the form of therapy that will work best for them. Dr. Sotsky reported that his data analysis provided “indirect evidence of treatment specificity by identifying characteristics responsive to different modalities, which may be of value in the selection of patients for alternative treatments.”¹¹³⁰

In terms of outcomes, the NIMH study reported that “there was a consistent ordering of treatments at termination, with imipramine plus clinical management generally doing best, placebo plus clinical management worst, and the two psychotherapies in between but generally closer to imipramine plus clinical management.”^{1131 1132} Dr.

¹¹²⁸Krupnick J, Sotsky S, Simmens S, Moyer J, Elkin I, Watkins J, Pilkonis P. The role of the therapeutic alliance in psychotherapy and pharmacotherapy outcome: findings in the National Institute of Mental Health Treatment of Depression Collaborative Research Program. *J Consult Clin Psychol* 64(Jun 1996) 3:532-9. see also O'Malley S, Foley S, Rounsaville B, Watkins J, Sotsky S, Imber S, Elkin I. Therapist competence and patient outcome in interpersonal psychotherapy of depression. *J Consult Clin Psychol* 56 (Aug 1988) 4:496-501.

¹¹²⁹Blatt S, Sanislow C, Zuroff D, Pilkonis P. Characteristics of effective therapists: further analyses of data from the National Institute of Mental Health Treatment of Depression Collaborative Research Program. *J Consult Clin Psychol* 64 (Dec 1996) 6:1276-84. According to the study, “more effective therapists are more psychologically minded, eschew biological interventions (i.e., medication and electroconvulsive therapy) in their ordinary clinical practice, and expect outpatient treatment of depression to take longer than did moderately and less effective therapists.”

¹¹³⁰ Sotsky S, Glass D, Shea M, Pilkonis P, Collins J, Elkin I, Watkins J, Imber S, Leber W, Moyer J, et al. Patient predictors of response to psychotherapy and pharmacotherapy: findings in the NIMH Treatment of Depression Collaborative Research Program. *Am J Psychiat* 148 (Aug 1991) 8:997.

¹¹³¹Elkin et al. (1989): 971.

¹¹³² For additional research based on data from the NIMH Collaborative study, see; Elkin I, Gibbons R, Shea M, Sotsky S, Watkins J, Pilkonis P, Hedeker D. Initial severity and differential treatment outcome in the National Institute of Mental Health Treatment of Depression Collaborative Research Program. *J Consult Clin Psychol* 63(Oct 1995) 5:841-7. and Agosti V, Ocepek-Welikson K. The efficacy of imipramine and psychotherapy in early-onset chronic depression: a reanalysis of the National Institute of Mental health Treatment of Depression Collaborative Research Program. *J Affect Disord* 43(May 1997)

Freedman commented on the results of the study by noting, “The observation that psychological supports as well as particular therapies can aid should signal to all physicians that the management of proved pharmacotherapies can be assisted by prudent supportive approaches.”¹¹³³ The finding that the combination of pharmacological interventions with clinical management performed the best is encouraging. It suggests that the combination of pharmacological and non-pharmacological variables involved in psychedelic psychotherapy may have additive therapeutic benefits.

A recent meta-analysis that included the NIMH data as well as data from other studies resulted in additional evidence supporting the increased efficacy of psychotherapy plus pharmacotherapy over psychotherapy alone in the treatment of major depression.¹¹³⁴ Non-significant trends suggesting the value of the combination of pharmacotherapy with cognitive therapy over either treatment alone were noted in another study in depressed patients.¹¹³⁵ In 80 patients suffering from bereavement-related depression, the combination of psychotherapy with pharmacotherapy as compared to either psychotherapy or pharmacotherapy alone demonstrated a significantly increased retention in treatment, with non-significant trends toward improved outcome.¹¹³⁶ These studies demonstrate that it is both potentially promising and methodologically feasible to standardize and evaluate psychedelic psychotherapy in comparison with different forms of psychotherapy as well as traditional pharmacotherapy alone or in combination with psychotherapy. Through a series of comparative studies utilizing standardized psychedelic psychotherapy, it may eventually

3:181-6; Stewart J, Garfinkel R, Nunes E, Donovan S, Klein D. Atypical features and treatment response in the National Institute of Mental Health Treatment of Depression Collaborative Research Program. *J Clin Psychopharmacol* 18 (Dec 1998) 6:429-34.

¹¹³³Freedman (1989): 983.

¹¹³⁴Thase M, Greenhouse J, Frank E, Reynolds C, Pilkonis P, Hurley K, Grochocinski V, Kupfer D. Treatment of major depression with psychotherapy or psychotherapy-pharmacotherapy combinations. *Arch Gen Psychiat* 54 (Nov 1997) 11:1009-15. According to the authors of this study, “Whereas combined therapy was not significantly more effective than psychotherapy alone in milder depressions, a highly significant advantage was observed in more severe recurrent depressions...Using this method, we found new evidence in support of the widespread clinical impression that combined therapy is superior to psychotherapy alone for treatment of more severe, recurrent depressions.”

¹¹³⁵Hollon S, DeRubeis R, Evans M, Wiemer M, Garvey M, Grove W, Tuason V. Cognitive therapy and pharmacotherapy for depression. Singly and in combination. *Arch Gen Psychiat* 49 (Oct 1992) 10:774-81. According to the authors, “Combining cognitive therapy with pharmacotherapy did not markedly improve response over that observed for either modality alone, although such nonsignificant differences as were evident did favor the combined treatment.”

¹¹³⁶Reynolds C, Miller M, Pasternak R, Frank E, Perel J, Cornes C, Houck P, Mazumdar S, Dew M, Kupfer D. Treatment of bereavement-related major depressive episodes in later life: a controlled study of acute and continuation treatment with nortriptyline and interpersonal psychotherapy. *Am J Psychiat* 156 (Feb1999) 2:202-8.

be possible to identify for specific types of patients the most effective non-pharmacological variables to use in combination with psychedelic drugs.

Psychedelic Psychotherapy Protocol Design Recommendations: Drs. Jones and O'Brien

In 1993, Sandoz Pharmaceutical Company, in association with the Swiss Academy of Medical Sciences, convened a small international conference to commemorate the 50th anniversary of the discovery of LSD. The conference was intended to honor Dr. Albert Hofmann, the Swiss scientist who first synthesized LSD.¹¹³⁷ The goal of the conference was to review the literature on LSD to date, summarize the findings, and suggest possible future directions for research. Papers presented at the conference were collected into a book.¹¹³⁸

Dr. Reese Jones, UC San Francisco, one of the pioneers of psychedelic research, and Dr. Charles O'Brien, University of Pennsylvania, an expert in psychotherapy outcome research, joined together to offer a discussion about methodological issues in the design of psychedelic psychotherapy protocols. Their fundamental point was that, "Measuring efficacy for combinations of medications and psychotherapy has proven more difficult but not impossible. Claims that medications such as LSD enhance the effects of psychotherapy can be evaluated using modern psychotherapy research techniques."¹¹³⁹ They emphasized the following eight essential characteristics of an adequate study: 1) specific diagnosis, 2) severity measures, 3) informed consent about risks v. benefits, 4) placebo control group, 5) random assignment, 6) standardized psychotherapy, manual guided, supervised with measured 'dose' of psychotherapy, 7) objective 'blind' raters, 8) importance of follow-up.¹¹⁴⁰

They recommended a placebo control group, but noted, "An obvious difficulty with evaluating a treatment such as an hallucinogen is that the patients and the raters will probably know who is receiving placebo and not the active medication. This may not be entirely unavoidable. First, there is the possibility of using an active placebo design, as was applied by Reginald Smart and colleagues when methylphenidate [Ritalin] and LSD were compared in the treatment of alcoholics. Another possibility is to use a very low dose of the active medication."¹¹⁴¹

¹¹³⁷Hofmann A. *LSD- My Problem Child*. New York: McGraw-Hill, 1980.

¹¹³⁸Pletscher A, Ladewig D. (eds.) *50 Years of LSD- Current Status and Perspectives of Hallucinogens.- A Symposium of the Swiss Academy of Medical Sciences*. Lugana-Agno, Switzerland, Oct. 21-22, 1993. New York: Parthenon Publishing Group, 1994.

¹¹³⁹O'Brien C, Jones R. Methodological issues in the evaluation of a medication for its potential benefits in enhancing psychotherapy. in Pletscher A, Ladewig D. (eds.) *50 Years of LSD- Current Status and Perspectives of Hallucinogens.- A Symposium of the Swiss Academy of Medical Sciences*. Lugana-Agno, Switzerland, Oct. 21-22, 1993. New York: Parthenon Publishing Group, 1994: 214.

¹¹⁴⁰*Ibid.*, 215.

As previously noted, Dr. Smart had used ephedrine, a stimulant similar to methylphenidate, as an active control in his LSD research. Unfortunately, he had found it to be ineffective as an active control. This makes it likely that methylphenidate would be similarly ineffective. Dr. Jones confirmed that methylphenidate had been ineffective as an active control in Dr. Smart's research and noted:

The Ritalin was not much better than the ephedrine as an adequate placebo for maintaining a double-blind treatment condition. On the other hand, either one or the other is probably better than no attempt at all to have some sort of comparison or control condition.

How important or imperfect the placebo can be before it becomes a useless exercise depends a lot on the hypothesis being tested and the non-drug considerations (setting, etc.) in the experiment and, in the case of LSD, the dose(s) being investigated. For low doses of LSD (maybe <75 micrograms or about 50), either stimulant might be more appropriate than if >100 micrograms of LSD was the treatment condition being studied.

The use of a "low" dose of the psychedelic as an active control is a possible alternative, particularly if the hypothesis allows for consideration of a dose-effect function. The trouble is that for many hypotheses I am not certain we know for certain what a low dose of LSD really is—i.e. what is the pharmacologic threshold for a certain or particular treatment effect?¹¹⁴²

In their article, Drs. O'Brien and Jones suggest a four-arm study with one group receiving only a placebo, a second group receiving only the psychedelic drug without psychotherapy, a third group receiving psychotherapy plus placebo, and the fourth group receiving the complete package of psychotherapy plus the psychedelic. They acknowledged the cost of such a design but suggested that a definitive study of this sort was necessary to sort out the relative contributions of two treatments, the psychotherapy and the psychedelic, each of which have their own independent effectiveness, with the possibility of a synergistic effect.¹¹⁴³

Though elegant in principle, one problem with this proposed design is the suggestion that a group of subjects receive only the psychedelic drug without psychotherapy. Drs. Ludwig, Levin and Stark made the same suggestion. As noted before,

¹¹⁴¹Ibid., 217.

¹¹⁴²personal communication, Dr. Reese Jones, March 14, 2000.

¹¹⁴³Hollon S, Shelton R, Loosen P. Research Considerations in Evaluating Combined Treatment. in (eds.) Beitman B, Klerman G. *Integrating Pharmacotherapy and Psychotherapy*. Washington, DC: American Psychiatric Press, 1991: 372.

there are ethical complications resulting from exposing a patient with a mental condition or disorder to the powerful effects of a psychedelic drug without offering any psychological counseling or assistance during the acute phase of the psychedelic effects. There is a distinct possibility that a powerful dose of a psychedelic administered to a patient with a mental condition or disorder in a clinical research setting could catalyze the emergence of difficult, problematic emotional material. In a therapeutic context this would be welcomed but the condition of the patient could significantly worsen if supportive psychotherapy was not administered. Due to the possibility of significant adverse effects, it would be unethical to administer a powerful psychedelic drug to a patient with a mental condition or disorder in the absence of supportive psychotherapy. For ethical reasons, there should be no psychedelic-only group. This leaves a three-arm study.

The suggestion that the research design include a group of patients who receive only placebo medication with no psychotherapy raises both ethical and methodological issues. Most importantly, the practical value of a placebo medication group with no psychotherapy is substantially reduced due to the fact that the subjects receiving the placebo would almost certainly be able to determine that they had received a placebo and not a full-dose of a psychedelic drug, breaking the blind. Furthermore, if there are either approved pharmacological treatments or psychotherapeutic treatments considered to have some degree of efficacy for the treatment of the patients' clinical condition, the ethical aspects of randomizing subjects to a placebo group would need to be addressed. This would depend on the severity of the condition if left untreated for the duration of the experiment. The use of patients who have failed on standard treatments would help address this ethical issue, since it is not unethical to randomize subjects who are non-responsive to treatment to a placebo condition, but then the results of the study would not necessarily generalize to all patients.

Assessing the likely value of the information to be gained from a non-blind placebo group that receives no psychotherapy would help determine whether it is possible to justify both the expense of including a placebo-only group in a study and the discomfort to be experienced by those patients who would receive only a placebo but could otherwise be randomized to a psychotherapy-only treatment group that might offer some incremental efficacy. On the one hand, the use of a placebo medication group would theoretically help generate information on the strength of the placebo effect. The extent of the placebo response could then be subtracted from the response of the subjects in the other groups to determine the value over and above the placebo effect of psychotherapy-only and psychotherapy in combination with a psychedelic. On the other hand, the certain failure of the placebo condition to remain blinded is likely to bias the estimation of the placebo effect. Even if the placebo effect could be estimated precisely in this context, which it can't, this information is of little practical value, since the placebo effect will always play a role in whatever treatment is being delivered. In the real world of resource constraints and real human beings as patients, the arguments for omitting a placebo-only group that would not

be blind in practice are more compelling than the arguments for including it.

This leaves a two-arm study in which the psychedelic psychotherapy condition would be compared to psychotherapy plus placebo. As indicated earlier, this is a higher standard than comparing psychedelic psychotherapy to a placebo-only group.

The suggestion that there be a psychotherapy plus placebo group is based on the assumption that there may be some therapeutic efficacy to the psychotherapy component of psychedelic psychotherapy, independent of the drug. The difficulty lies in trying to conduct a single or double-blind investigation of the psychotherapy-only condition. In the psychotherapy plus placebo group, an inactive placebo would not be effective in producing a single or double-blind. As for an active placebo, it might have side effects and a risk profile of its own that might not be comfortable to patients with a mental condition or disorder. Even with an active placebo, the chances of creating an effective single or double-blind seem remote, since the proposed design calls for a full therapeutic dose of the psychedelic drug. Even active placebos can be distinguished from full therapeutic doses of a psychedelic drug by most patients and experimenters.

In the NIMH Collaborative Study of Depression, no attempt was made to create a double-blind between the two psychotherapy treatment arms and the pharmacotherapy arms, yet the groups/treatments were successfully and repeatedly compared with each other in a succession of studies. This indicates that the lack of a double-blind between the psychotherapy-only group and the psychedelic psychotherapy group is not necessarily a fundamental design flaw when attempting to compare the efficacy of different treatments.

The core of the recommendation made by Drs. O'Brien and Jones for the evaluation of psychedelic psychotherapy is the need to compare psychedelic psychotherapy with the identical psychotherapy without the psychedelic. Whether the psychotherapy-only group is administered a placebo medication, either inactive or active, or no placebo at all, will be discussed in Chapter 5, but is of secondary importance to the fundamental need to compare psychedelic psychotherapy to the identical psychotherapy without the psychedelic drug.

Conclusion: Standards of Proof and the Two-Arm Study

This chapter's review of the relevant regulatory, ethical and methodological issues related to standards of proof and protocol designs for the evaluation of psychedelic psychotherapy was conducted in order to answer two questions. The first question is whether the standard of proof normally used by FDA for the evaluation of the safety and efficacy of new drugs, a comparison of test drug to placebo, is sufficient for the evaluation of psychedelic psychotherapy. The answer proposed in this chapter is that FDA's normal standard of proof is sufficient and that there is no justification for imposing a higher standard for FDA's review of studies with psychedelic drugs than for other drugs regulated by FDA. This conclusion is similar to the 1992 recommendation of FDA's Drug Abuse Advisory Committee that led to the establishment of FDA's currently-held policy that there is no need to impose a higher standard for the approval of research protocols with

psychedelic drugs than for protocols testing other drugs.

The second question analyzed in this chapter concerns the appropriate protocol design for the evaluation of psychedelic psychotherapy. After careful methodological analysis, the recommended protocol design is a basic two-arm study, with one arm being the full-dose psychedelic psychotherapy treatment and the other arm being the psychotherapy-alone “placebo” treatment.

Does Political Controversy Justify Higher Standards?

The mere fact of political controversy concerning the medical use of psychedelics and marijuana does not provide sufficient analytical justification for the requirement that higher standards of proof be imposed on this class of drugs. While higher standards for the review of the medical uses of psychedelics and marijuana cannot be justified due to political controversy alone, they may still be required by political factors. As a result, it may still make sense for sponsors of the medical use of these drugs voluntarily to design efficacy trials so that psychedelics are tested against a psychotherapy-only control group as well as against an active control consisting of the best available medicine approved for similar patient populations.

At the February 1997 meeting of the NIH Expert Committee on the Medical Utility of Marijuana,¹¹⁴⁴ Dr. Temple, Associate Director for Medical Policy, CDER/FDA, delivered a talk entitled, “Clinical Trial Considerations with Marijuana.”¹¹⁴⁵ Dr. Temple explained FDA’s official policy that drugs need only be compared to placebo to determine efficacy, but observed that due to the intense political controversy over the medical use of marijuana, it would be wise also to compare marijuana against the best available medicine for each specific clinical indication being treated.

Chapter 5 examines how Dr. Temple’s sage advice about the need to take political factors into account can be translated into specific protocol designs for the evaluation of psychedelic psychotherapy.

¹¹⁴⁴Ad Hoc Group of Experts. Workshop on the Medical Utility of Marijuana: Report to the Director, National Institutes of Health, February 19-21, 1997.
<http://www.nih.gov/news/medmarijuana/MedicalMarijuana.htm>

¹¹⁴⁵This talk has not been published, but Dr. Temple has given out copies of his slides. Quotes attributed to Dr. Temple are from these slides. Dr. Temple acknowledged the contributions of Dr. Curtis Wright to the content of his talk.