

CHAPTER 5  
ENHANCED PROTOCOL DESIGNS FOR EVALUATING  
PSYCHEDELIC PSYCHOTHERAPY

In Chapter 4, a standard of proof was proposed for use by FDA in evaluating psychedelic psychotherapy for approval for prescription use. That standard was the comparison of psychedelic psychotherapy with the identical psychotherapy without a psychedelic drug, either with or without active or inactive placebo. In such a two-arm study, psychedelic psychotherapy would need to be shown statistically more effective than the identical psychotherapy without the use of a psychedelic drug in order for a psychedelic to be approved as a prescription medicine. This standard was developed after thorough consideration of arguments concerning, 1) the high potential for abuse of psychedelics, 2) the possible impact of the approval of psychedelic psychotherapy on the non-medical use of psychedelics, 3) ethical concerns related to the value of providing patients with a wider choice of medications, 4) ethical concerns about the use of placebo controls in patients in need of treatment, and 5) methodological considerations resulting from the practical failure to achieve a double-blind in studies using psychedelic drugs.

In this chapter, a proposal is made for the use of a more rigorous template for the “adequate and well controlled investigations” required for the evaluation of psychedelic psychotherapy. This proposal takes yet another factor into account, the political reality of significant opposition, based on both rational and irrational grounds, against the medical use of any Schedule I drug, especially psychedelics and marijuana.<sup>1146</sup> This chapter begins with a discussion and critical review of the protocol designs of all currently approved studies worldwide investigating psychedelic psychotherapy in patient populations. The chapter then proposes several enhancements and elaborations to the two-arm study design proposed in

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<sup>1146</sup> The impact of political factors on science and medicine as it relates to psychedelic psychotherapy research is unavoidable, especially around the time when the front page of *USA Today* features an article with the headline, “Feds Crack Down on Ecstasy [MDMA]- Health fears, Organized Crime put drug on map,” and the entire second page of the paper is also about MDMA, with the headline, “ ‘Party’s Over’: Studies show drug causes brain damage. Leinwand D, Fields G. Feds Crack Down on Ecstasy. *USA Today*. April 19, 2000: A1. In the article, Dr. Alan Leshner, Director of the National Institute on Drug Abuse, was quoted as saying, “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 kids. We’re trying to use science to get in the way of a potential public health plague.” Leinwand D, Fields G. ‘Party’s Over’: Studies show drug causes brain damage. April 19, 2000:A2. Needless to say, the science that Dr. Leshner is talking about is focused on the risks of MDMA and not on its benefits as an adjunct to psychotherapy. Within the same week, the television news show 60 Minutes II featured as its lead story the use of MDMA by young people at all night dance parties called raves, presenting the growing popularity of MDMA in alarming and breathless terms. 60 Minutes II, Tuesday, April 25, 2000. Finally, a balanced article was written, as a Time cover story. Cloud J. The Lure of Ecstasy. *Time Magazine*(June 5, 2000): 62-68.

Chapter 4. The recommendation of Dr. Robert Temple, Associate Director for Medical Policy, CDER/FDA to “over-design,”<sup>1147</sup> made in the context of a discussion on designing clinical trials to evaluate the medical use of marijuana, is taken to heart.

The end result is a proposal for a four-arm study, with three arms used for a dose-response study of psychedelic psychotherapy. The lowest-dose arm of the dose-response portion of the study utilizes a sub-threshold dose of the psychedelic drug being tested, thus serving as the psychotherapy-only control condition with the placebo effect maximized. The second arm of the dose-response study is psychedelic psychotherapy utilizing a medium dose of the psychedelic being tested. The third arm is psychedelic psychotherapy utilizing a full-dose. The fourth arm is a parallel evaluation of the most effective current treatment for the clinical indication being studied, permitting a comparison between psychedelic psychotherapy and the most effective alternative treatment.

This chapter concludes with an analysis of the costs of drug development for psychedelic psychotherapy. The analysis demonstrates that the proposed criteria for the design of psychedelic psychotherapy research protocols do not impose an unreasonable burden on sponsors interested in evaluating these medical uses.

Chapter 6 concludes the dissertation with a discussion, well in advance of any practical necessity, of a system of regulatory controls designed to minimize potential abuse, misuse and diversion of psychedelics if any eventually do become approved as prescription medicines.

#### Background: Currently Approved Psychedelic Psychotherapy Studies

As of April 2000, scientific research into the therapeutic use of psychedelic drugs in patient populations has been approved in three countries: Russia, Spain and the United States. In January 2000, Dr. Evgeny Krupitsky, St. Petersburg (Russia) Scientific Research Center for Addictions and Psychopharmacology, began a five-year study in eighty heroin addicts evaluating the use of multiple (three) sessions of high-dose ketamine-assisted psychotherapy as compared to a single session. Dr. Krupitsky is receiving financial support from two non-profit organizations, MAPS and the Heffter Research Institute (HRI). Dr. Krupitsky previously conducted a three-year study demonstrating that a single high dose session was more effective than an active placebo (low-dose ketamine) in promoting abstinence and recovery in heroin addicts.<sup>1148 1149</sup> On February 7, 2000, the Spanish Ministry of Health approved a protocol submitted by Jose Carlos Bouso Saiz and Dr. Pedro Antonio Sopelana Rodríguez, University Autonoma de Madrid, designed to test the use of MDMA-assisted psychotherapy in the treatment of twenty-nine women who suffer from chronic post-traumatic stress disorder (PTSD) as a result of sexual assault.<sup>1150 1151</sup> This

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<sup>1147</sup>Dr. Temple, NIH Workshop on the Medical Utility of Marijuana, Slide 26, “Remedies, potential.”

<sup>1148</sup>Krupitsky (1999).

<sup>1149</sup>Krupitsky 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.

study, to be funded by MAPS, will be the first government-approved, controlled scientific study ever conducted worldwide into the therapeutic use of MDMA in any patient population.<sup>1152</sup> In the United States, Dr. John Krystal and associates at Yale Medical School published a pilot study in February 2000 showing the effectiveness of ketamine without associated psychotherapy in temporarily reducing depressive symptoms in seven depressed patients.<sup>1153</sup> Though they generated some promising results, they were conducting a theoretical investigation of the effects of stimulating various brain neurotransmitters and are not seeking to develop ketamine for use in depressed patients. Their study received support from NIMH. Drs. Pedro Delgado and Francisco Moreno, University of Arizona Medical

<sup>1150</sup>Farnell, Josep Torrent i. Director, Spanish Agency of Medicine, (AEM-Agencia Española del Medicamento) Spanish Ministry of Health and Consumer Affairs. Letter to Jose Carlos Bouso Diaz. Reference # 447. Spanish Drug Agency Code Protocol # 99-0309. February 7, 2000. Administration of 3,4 Methylendioxy-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.

<sup>1151</sup>Bouso J. Proposal for a Study with MDMA and Post Traumatic Stress Disorder in Spain. *Bull MAPS* 9 (Autumn 1999) 3:11-14. <http://www.maps.org/news-letters/v09n3/09311bou.html>

<sup>1152</sup>No controlled scientific studies into the therapeutic use of MDMA were conducted before July 1, 1985, when MDMA was still unscheduled. A collection of self-reported experiences with MDMA before its scheduling has been published; Adamson S, Metzner R. *Through the Gateway of the Heart*. San Francisco: Four Trees Publications, 1985. A series of case reports based on treatments conducted prior to the scheduling of MDMA was published by Dr. George Greer and Requa Tolbert R.N. in Greer G, Tolbert R. Subjective Reports of the Effects of MDMA in a Clinical Setting. *J Psychoact Drug* 18 (1986) 4:319-327 (full text: <http://www.heffter.org/SUBJREPT.HTML>). A subsequent chapter and article described their method, Greer G, Tolbert R. The therapeutic use of MDMA. in Peroutka S (ed.) *Ecstasy: The Clinical, Pharmacological and Neurotoxicological Effects of the Drug MDMA* Norwell, MA: Kluwer Academic Publishers, 1990. Greer G, Tolbert R. A Method of Conducting Therapeutic Sessions with MDMA. *J Psychoact Drug* 30 (1998) 4:371-379. An additional case report was written by Wolfson P. Meetings at the Edge with Adam: A man for all seasons? *J Psychoact Drug* 18 (1986) 4:329-333. An article discussing a post-treatment non-anonymous self-report survey of some of the patients who had undergone MDMA-assisted psychotherapy in Switzerland from 1988-1993 has been published. Gasser P. Psycholytic therapy with MDMA and LSD in Switzerland: Follow-up study on the results of Swiss research conducted during 1988-1993. *Bull MAPS* 5 (Winter 1994-95) 3:3-7. <http://www.maps.org/news-letters/v05n3/05303psy.html> One of the Swiss psychiatrists has published a book about the therapeutic use of MDMA. Widmer S. *Listening Into the Heart of Things: The Awakening of Love On MDMA and LSD: the Undesired Psychotherapy*. Gerolfingen, Switzerland: Basic Editions, 1995.

<sup>1153</sup>Berman R, Cappiello A, Anand A, Oren D, Heninger G, Charney D, Krystal J. Antidepressant effects of ketamine in depressed patients. *Biol Psychiat* 47 (Feb 2000) 4:351-4.

School, expect to begin around September 2000 to investigate the potential efficacy of psilocybin as a treatment for obsessive-compulsive disorders in an FDA-approved pilot study involving ten patients. Drs. Delgado and Moreno are receiving support from MAPS and HRI.<sup>1154</sup> The mechanism of action they are exploring is based on psilocybin's pharmacological rather than psychological effects.<sup>1155</sup>

Approvals of additional psychedelic psychotherapy research protocols are likely, with several projects already in the protocol design and approval process. Dr. Charles Grob, Harbor-UCLA, is working with the support of MAPS to design and obtain approval for a study of MDMA in the psychotherapeutic treatment of cancer patients.<sup>1156</sup> Dr. Moshe Kotler and Dr. Adam Darnell, Ben-Gurion University of the Negev, Israel, are developing a protocol with support from MAPS to study the use of MDMA in the treatment of PTSD.<sup>1157</sup> Dr. Richard Yensen, Orenda Institute, Baltimore, MD, is working with support from non-profit organizations to design and obtain approval for a study of the use of LSD in the psychotherapeutic treatment of cancer patients.<sup>1158</sup> Dr. Franz Vollenweider, University of Zürich, is working with support from HRI to obtain approval to study the use of psilocybin-assisted psychotherapy in the treatment of depression.<sup>1159</sup> Dr. Ken Alper, New York University, is working with the support of private investors to obtain permission outside of the United States to study the use of ibogaine in the treatment of opiate withdrawal.<sup>1160</sup> Dr. Moshe Kotler, Ben-Gurion University of the Negev, Israel is working with support from a private for-profit company, Humatech, Inc., to obtain permission to study ibogaine in the treatment of opiate withdrawal.<sup>1161</sup> It is possible that other projects are

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<sup>1154</sup>IND # 56,530. The study was approved in a Sept 17, 1998 letter from Dr. Cynthia McCormick, Director FDA's DACCADP, to Dr. Francisco Moreno, U. of Arizona, pending obtaining an FDA-approved supply of psilocybin. Difficulties in obtaining a source of FDA-approved research-grade psilocybin have delayed the start of the study, which is now estimated to be begin during Fall 2000.

<sup>1155</sup>For the theoretical basis of this research, see Delgado P, Moreno F. Hallucinogens, Serotonin and Obsessive-Compulsive Disorder. *J Psychoact Drug* 30 (Oct-Dec 1998) 4:359-366; Delgado P, Moreno F. Different roles for serotonin in anti-obsessional drug action and the pathophysiology of obsessive-compulsive disorder. *Br J Psychiatry* (1998) Suppl. 35:21-5; Moreno F, Delgado P. Hallucinogen-induced relief of obsessions and compulsions. *Am J Psychiat* 154 (Jul 1997) 7:1037-8.

<sup>1156</sup>For information on the negotiations with FDA concerning this protocol, see <http://www.maps.org/research/mdma/0699mdma.html>.

<sup>1157</sup>Doblin R. Clinical Research with MDMA and MDE- A MAPS' Conference: Dead Sea, Israel. *Bull MAPS* 9 (Winter 1999 /2000) 4:2-9. <http://www.maps.org/news-letters/v09n4/09402dob.html>

<sup>1158</sup>personal communication, Richard Yensen, March 24, 2000.

<sup>1159</sup>Nichols D. The Heffter Research Institute: New Swiss Program. *MAPS* 9 (Winter 1999 / 2000) 4:49. <http://www.maps.org/news-letters/v09n4/09449hri.html>

<sup>1160</sup>personal communication, Dr. Ken Alper, March 30, 2000.

also in the development stages and are being conducted confidentially.

### Issues in Developing a Clinical Plan

A Clinical Plan outlines the proposed sequence of studies in humans that the sponsor of a drug will conduct in order to gather data on the drug's safety and efficacy.<sup>1162</sup> Animal toxicity studies establishing an acceptable safety profile for the intended use must precede the Clinical Plan. The studies specified in the Clinical Plan should be sufficient to enable both the sponsor of the research and the FDA to determine whether the drug should be approved for prescription use. The Clinical Plan is not set in stone but is modified in response to the data gathered in each stage of the research.

Phase I of a Clinical Plan is composed of basic safety studies, usually involving healthy subjects. Patients are rarely involved as subjects in Phase I studies unless the test drug has substantial toxicity, with a risk profile so great that it would be unethical to administer the drug to anyone but patients for whom the benefits may offset the risks, as is the case with new chemotherapy drugs. Dr. Lasagna elaborates that, "the purposes of the earliest trials in humans are (a) to assess "tolerability" for the drug and ascertain the dose that produces some sort of discernible effect (even if only toxic) in humans, and (b) to obtain information on the absorption, distribution, metabolism and excretion of the drug and any relationship between pharmacokinetic measurements and clinical effects."<sup>1163</sup>

Phase II is composed of preliminary studies in relatively small patient populations that explore efficacy as well as safety. Some of these studies need not be conducted in as rigorous a fashion as subsequent studies. Dr. Laska et al. explain, "The purpose of open trials, studies without blinding and usually without randomization, is to formulate hypotheses for later testing as to the role and method of use of the new agent."<sup>1164</sup>

Phase III is composed of larger studies that are intended to be the "adequate and well-controlled investigations" of safety and efficacy that form the basis of any request to FDA for approval for marketing. These studies need to be designed extremely carefully. Design flaws that introduce bias can invalidate the effort to draw conclusions from the data, which have been generated at substantial cost.

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<sup>1161</sup>personal communication, Bob Rand, President, Humatech Inc, March 5, 2000.

<sup>1162</sup>For a detailed discussion of the process of drug development for psychotropic drugs, see, Lasagna L. Decision Processes in Establishing the Efficacy and Safety of Psychotropic Agents. In (ed.) Prien R, Robinson D. *Clinical Evaluation of Psychotropic Drugs: Principles and Guidelines*. New York: Raven Press, 1994: 13-28. This edited volume was created in association with the National Institute on Mental Health (NIMH) and the American College of Neuropsychopharmacology (ACNP). Also, Laska E, Klein D, Lavori P, Levine J, Robinson D. Design Issues for the Clinical Evaluation of Psychotropic Drugs. in (ed.) Prien R, Robinson D. *Clinical Evaluation of Psychotropic Drugs: Principles and Guidelines*. New York: Raven Press, 1994: 29-67.

<sup>1163</sup>Lasagna (1994): 16.

<sup>1164</sup>Laska et al. (1994): 36.

Phase IV studies are conducted after the approval of the compound for marketing. These studies are designed to expand the knowledge base about issues of safety and efficacy. With most drugs, too few subjects are enrolled in the clinical trials that are used as a basis for approval to ensure that rare reactions and unusual adverse effects have been identified. Many Phase IV studies are designed to gather additional safety information on a wider range of patients. With Schedule I drugs, the situation is reversed. Many of these drugs have been taken recreationally by millions of people, with the scientific literature filled with reports of rare and unusual adverse reactions. More is known about the safety/risk profile of Schedule I drugs than about their efficacy, in contrast to new prescription drugs, where more is known about their efficacy than about their safety/risk profile.

#### Phase I Safety Studies—Dose-Escalation Designs

Phase I safety studies examine the effects of doses ranging from well below the expected therapeutic dose to slightly higher than the expected therapeutic dose. The higher doses may cause the subjects some mild discomfort but should not result in any temporary or permanent harm. Since psychedelic research was resumed in the United States in 1990, basic Phase I safety studies have been completed only for DMT<sup>1165</sup> and MDMA.<sup>1166</sup> A Phase I safety study was approved by FDA for psilocybin and was partially implemented. The study was halted as a result of the principal investigator moving for family reasons from the United States to Canada.<sup>1167</sup> An FDA-approved safety study of ibogaine was also started but was abandoned for lack of funds.<sup>1168</sup>

The protocols in the Phase I safety studies with DMT, MDMA, psilocybin and

<sup>1165</sup>Strassman R, Qualls C. Dose-response study of N,N-dimethyltryptamine in humans. I. Neuroendocrine, autonomic, and cardiovascular effects. *Arch Gen Psychiat* 51 (Feb 1994) 2:85-97; Strassman R, Qualls C, Uhlenhuth E, Kellner R. Dose-response study of N,N-dimethyltryptamine in humans. II. Subjective effects and preliminary results of a new rating scale. *Arch Gen Psychiat* 51 (Feb 1994) 2:98-108; Strassman R. Human psychopharmacology of N,N-dimethyltryptamine. *Behav Brain Res* 73 (1996) 1-2:121-4; Strassman R, Qualls C, Berg L. Differential tolerance to biological and subjective effects of four closely spaced doses of N,N-dimethyltryptamine in humans. *Biol Psychiat* 39 (May 1, 1996) 9:784-95.

<sup>1166</sup>Grob 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. See also Chang L, Grob C, Ernst T, Itti L, Mishkin S, Jose-Melchor R, Poland R. Effect of ecstasy [3,4-methylenedioxymethamphetamine (MDMA)] on cerebral blood flow: a co-registered SPECT and MRI study. *Psychiat Res* 98 (Feb 200) 1:15-28.

<sup>1167</sup>personal communication, Rick Strassman, February 4, 1998. Approved August 10, 1994. IND #39258. A Phase I dose- response safety study to be conducted by Dr. Rick Strassman, U. of New Mexico Medical School.

<sup>1168</sup>Staff. Data Accrue on “Visionary” agent to interrupt addiction. *Lancet* 354 (November 27, 1999): 1883.

ibogaine were of a similar design. This design consisted of a dose-escalation study in healthy subjects (not patients).<sup>1169</sup> One variation of this design was used in the DMT and psilocybin studies, both designed and conducted by psychedelic researcher Dr. Rick Strassman. All subjects were to be administered all four different dose levels of the test drug or inactive placebo in a randomized, double-blind manner, with each administration taking place at least a week apart. In the DMT study, all eleven subjects first received two unblinded sessions in which they received a low dose of DMT and then a high dose, in order to prepare them psychologically for the random administration of the full range of doses used in the blinded portion of the study.<sup>1170</sup> The psilocybin study was designed in almost the same way, however, all subjects would have first received a low dose of DMT and then a high dose of DMT in two non-blind sessions. According to Dr. Strassman, “that way, we’d see how they did seriously intoxicated for a short trip, before we all committed to a longer one.”<sup>1171</sup> Prior to participating in the double-blind portion of the study, subjects would have also received a low dose of psilocybin non-blind, and a high dose non-blind. Dr. Strassman reported that actual administration “only got to determining what would be a high dose and a low dose.”<sup>1172</sup>

In another variation of the dose-escalation design, used in the MDMA and ibogaine studies, a small number of subjects (six in both studies) received either one or two doses of the test drug. In the ibogaine study, subjects participated in two sessions spaced at least a week apart. Subjects were randomly administered in a double-blind manner either a dose of ibogaine or inactive placebo. In the MDMA study, subjects participated in three sessions in which they were randomly administered in a double-blind manner either two slightly different doses of MDMA (separated by 0.25 mg/kg) or inactive placebo. In both studies, if no serious adverse effects were noticed after the initial group of subjects had been exposed to the lowest doses, another group of subjects would be administered incrementally higher doses. The process of testing new groups at successively higher doses was to continue until the highest dose was administered. The MDMA study involved nine different doses of MDMA and 18 subjects. The ibogaine study would have evaluated the effects of a similar number of different doses in about 50 subjects if it had been completed. Only two different dose levels were actually administered before funds ran out.

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<sup>1169</sup>Due to a reluctance to introduce drug-naïve subjects to drugs with a potential for abuse, subjects in the MDMA study were required to have had prior experience with MDMA in non-medical settings. In the other studies, subjects were required to have prior experience with the test drug or similar psychedelics. This inclusion criterion ensured that no drug-naïve subjects would be motivated to use these drugs non-medically as a result of being first exposed in a clinical research setting.

<sup>1170</sup>Strassman R, Qualls C. Dose-response study of N,N-dimethyltryptamine in humans. I. Neuroendocrine, autonomic, and cardiovascular effects. *Arch Gen Psychiat* 51 (February 1994) 2:85-97.

<sup>1171</sup>personal communication, Dr. Strassman, April 5, 2000.

<sup>1172</sup>personal communication, Dr. Strassman, April 5, 2000.

In all these Phase I studies, the administration of an inactive placebo was included in the design. The use of an inactive placebo raises no ethical issues in Phase I studies in healthy subjects. These subjects are not in need of treatment, therefore no treatment is denied to those subjects receiving a placebo. Inactive placebos can be effective in producing a double-blind situation in preliminary dose-escalation studies, though only in the early stages when the lower doses are being tested.

In 1996, Dr. Strassman wrote, “The first stage in the resumption of human research with psychedelics is complete. This work, taking place in the United States, Europe and Russia, has established the safety of administering these highly restricted medications to humans...The nature of the appropriate placebo or control condition in psychotherapy studies continues to plague investigators.”<sup>1173</sup>

### Phase II Preliminary Safety/Efficacy Studies- Dose-Escalation Designs

A Phase II study is designed to initiate research in a patient population that is hypothesized to benefit from the new drug. One purpose of the Phase II study is to gather preliminary information about whether the test drug can be given safely to the particular patient population being studied. Another purpose is to gather preliminary evidence of efficacy to aid in the choice of the appropriate therapeutic doses and sample sizes that will be used in subsequent Phase III studies, if there are to be any. In the case of psychedelic research, other important functions of Phase II studies are to give the therapeutic teams the opportunity to develop their skills administering psychedelics to patient populations and to familiarize researchers and regulatory agencies with the specific issues involved in the design, implementation and interpretation of such protocols.

### The FDA-Approved Psilocybin/OCD Study

Dr. Moreno and Dr. Delgado, University of Arizona, are currently the only researchers in the United States with an FDA-approved Phase II protocol permitting the evaluation of the therapeutic use of a psychedelic drug in a patient population. Their study is designed to explore the administration of psilocybin to a maximum of ten patients with obsessive/compulsive disorder.<sup>1174</sup> According to the researchers, “Two important questions will be addressed in this protocol: 1) do potent 5-HT 2A/2C agonist hallucinogens lead to an acute decrease in the symptoms of OCD; 2) is a full hallucinogenic dose required to demonstrate significant reduction in the symptoms of OCD.”<sup>1175</sup>

The FDA approved this Phase II study even though the FDA-approved Phase I

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<sup>1173</sup>Strassman R. Issues in Psychedelic Research Introductory Comments: Psychedelic Research Panel, 1996 ITA Conference. *BULL MAPS* 7 (Winter 1996-97) 1:22-23. <http://www.maps.org/news-letters/v07n1/07122str.html>

<sup>1174</sup>IND # 56,530. Effects of Psilocybin in Obsessive-Compulsive Disorder. <http://www.maps.org/research/psilo/azproto.html>

<sup>1175</sup>Ibid.,1.

psilocybin safety study, proposed to FDA by Dr. Strassman, has not been completed. In approving the Phase II psilocybin study, the researchers and the FDA had available for review over 100 papers in the scientific literature reporting on data from studies conducted with psilocybin from the 1950s to the 1970s.<sup>1176</sup> These studies have previously established the safety of the use of psilocybin in humans in the context of controlled clinical trials. As an added safety precaution designed to reduce the chance that any subjects would have an adverse psychological reaction to the psilocybin, FDA required the subjects to have had at least one experience with a psychedelic drug within the previous ten years. The prior use of MDMA by subjects was not considered sufficient to qualify for entrance into the study due to MDMA's less challenging psychological effects than that of psilocybin and other classic psychedelics such as LSD and mescaline.

The Phase II psilocybin/OCD study employs a dose-escalation design, though it differs slightly from the Phase I dose-escalation designs previously discussed. Subjects will participate in a series of up to four treatment sessions, with two weeks between sessions. Subjects will be treated individually. Subjects will be administered a graduated sequence of a low (0.1 mg./kg), then moderate (0.2 mg/kg), then full dose (0.3 mg/kg) of psilocybin. If either beneficial or adverse effects are noted, no additional sessions will be administered. The session with a very low dose of psilocybin amounting to 1/4 of the lowest dose (0.025 mg/kg) will be scheduled randomly after the first 0.1 mg/kg dose. Depending on the sensitivity of the subjects, this very low dose will be either below or at the threshold of detection, with minimal effects if any.<sup>1177</sup> Dr. Moreno reported that the random

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<sup>1176</sup>The researchers reported in their IND application to FDA that, "A vast review of the literature including 101 scientific publications dating back to the 1950s was made available for us from Sandoz Pharmaceuticals." Sandoz Pharmaceuticals was the company that patented psilocybin and then kept a data base on all research conducted with the drug until the middle 1980s, well after their patent expired.

<sup>1177</sup> This exact amount of this very low dose of psilocybin, set at .025 mg/kg, will depend on the weight of the subjects. For subjects weighing between 60 and 100 kgs (132 to 220 lbs), the dose will range between 1.5 and 2.5 mgs. Dr. Pahnke wrote in an unpublished paper (Pahnke, W. Report on a pilot project investigating the pharmacological effects of psilocybin in normal volunteers. Massachusetts Mental Health Center. Unpublished manuscript. (1966). 1-5.) that 5 mgs. had a minimal effect and "was not an adequate control substance because the experience produced is so minimal that during the sessions both the experimenters and subjects could distinguish such reactions from those produced by a high dose of psilocybin." Dr. Shulgin (personal communication, April 5, 2000) reported that in his own self-experiments, 1.5 mgs had no effect while 3.0 mgs. resulted in only a slight tingling starting at 30 minutes and lasting until the 4 hour point. Dr. Nichols reported (personal communication, April 5, 2000) that, "My understanding is that a dose of 2.5 mg would be really hard to detect. I think 1.5 would probably be below threshold, and 2.5 might be just at or slightly below threshold." Dr. Vollenweider reported (personal communication, April 7, 2000), "psilocybin at doses between 1 and 2 mg have virtually no effects. What we found in a pilot study with 3 subjects was that 2 mg produces a very slight increase in awareness and visual perception, the overall effects were valued to be as similar as "a glass of wine."

administration of the very low dose was a protocol change requested by FDA, in order to “make sure the procedure was blinded so that people did not [automatically] report escalated effects as the doses escalated.”<sup>1178</sup>

One purpose to be served by this very low dose is to permit the informed consent form to state that the doses will be administered in a randomized, double-blind procedure, denying the subjects information they could use to predict the order of the doses to be administered. The second purpose is to make it difficult for the researchers to predict with certainty which dose they are giving to the subjects since the experimenters, but not the subjects, are aware that the three above-threshold doses will be administered in predictably escalating order. In actual practice, the effectiveness of this very low dose in introducing doubt into the ability of the experimenters to predict which dose will be administered depends on where in the sequence this dose is randomly administered. Once subjects have received this very low dose, which both subjects and experimenters will probably be able to identify by virtue of the absence or minimal nature of any effect, the experimenters can then predict that the remaining doses will be administered in a sequentially escalating order.

Though it may seem like the function of this very low dose could have been served equally well by an inactive placebo as by the very low dose of psilocybin, which will be either unnoticeable or barely noticeable, that is not the case. The important advantage of the use of a very low dose of psilocybin over the use of an inactive placebo is in maximizing the placebo effect. Subjects will be informed that they will receive at least some psilocybin on every occasion. With an inactive placebo, subjects would have been informed ahead of time that one dose would be inactive. As a result of the very low dose of psilocybin, subjects will assume that there is at least the possibility of some effect, however minimal, during each session. The informed consent form does not state what exact doses will be administered on any of the four session, only that some of the doses “may be enough to induce a hallucinogenic/psychedelic experience, and some of which may not.”<sup>1179</sup>

FDA’s recommendation to randomly administer a sub-threshold dose of the psilocybin within the predictably escalating sequence of low, medium and high doses was called, “an elegant design” by Dr. Jordi Riba, Area d’Investigació Farmacològica, Institute de Recerca, Hospital de Sant Pau, Barcelona.<sup>1180</sup> This design technique of using a very low sub-threshold dose to maximize the placebo effect without causing a direct pharmacological effect will be employed to enhance the psychotherapy control condition in the proposed four-arm study design that will be elaborated later in this chapter.

Another advantage, though minor, of using a very low dose of psilocybin instead of

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<sup>1178</sup>personal communication, Dr. Moreno, March 14, 2000.

<sup>1179</sup>IND # 56,530.Effects of Psilocybin in Obsessive-Compulsive Disorder. Informed Consent Form. <http://www.maps.org/research/psilo/azconsent.html>

<sup>1180</sup>personal communication, Dr. Riba, April 14, 2000. Dr. Riba is conducting controlled clinical research in healthy subjects with ayahuasca, a psychoactive mixture from the Amazon used in religious rituals, with permission from the Spanish Ministry of Health.

an inactive placebo is that a very low dose can still be plotted on a dose-response graph. Technically, there is no place to plot an inactive placebo (a zero dose) since dose/response graphs plot dose on the x-axis and the response of interest on the y-axis. A zero dose would need to be superimposed on the y-axis.<sup>1181</sup>

One general limitation of the use of a design in which all subjects receive all doses is the possibility that the effects of one dose will be long-lasting, with a subject not returning to baseline before the next scheduled session. If this occurs, the data to be gathered about the effects of the subsequent doses will be contaminated by the long-lasting effects of the previous dose. The experimenters address this concern in the psilocybin study by stating that the subjects will not move to higher doses if beneficial or adverse effects are noticed. This approach eliminates the possibility that the consequences of an earlier dose will be attributed to a subsequently higher dose. However, if a dose does produce a beneficial effect and the subject is not administered a higher dose, there is no way to determine if that subject would have benefited by the higher dose to a greater extent than by the lower dose. Given that this study is just a pilot study, this is not a serious problem, since any evidence of beneficial effects will likely result in subsequent studies.

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

There is only one Phase II dose-escalation study testing a psychedelic drug in a patient population currently approved anywhere outside of the United States. That study, coordinated by Jose Carlos Bouso, Ph.D. Candidate, University Autonoma de Madrid, will examine the use of MDMA in the treatment of 29 women suffering from PTSD as a consequence of sexual assault. Five different doses of MDMA will be evaluated, with sessions conducted individually. The design of this study differs from the psilocybin/OCD study in that each subject will participate in only one treatment session and will receive only one of the five different doses of MDMA being tested or an inactive placebo.

The first subgroup of four subjects will be administered either the lowest dose (50 mgs)<sup>1182</sup> or inactive placebo. Of these four subjects, three will receive the MDMA and one will receive the placebo, making the odds of receiving the MDMA (75%) larger than the odds of receiving the placebo (25%). If the entire first subgroup safely experiences the initial dose of MDMA or placebo, the members of a second subgroup will receive either the next higher dose of MDMA (75 mgs) or an inactive placebo, and so on. The second (75 mgs), third (100 mgs) and fourth (125 mgs) subgroups will each be composed of seven

<sup>1181</sup>personal communication, Dr. Nichols, April 5, 2000.

<sup>1182</sup>The dosing in this study is not based on the weight of the subjects in mgs/kg but is uniform for all subjects in each dose group, regardless of weight. Whether the subjective effects of MDMA actually vary significantly by weight is a matter of debate and has never been experimentally determined. As Dr. Strassman noted (personal communication, April 7, 2000), “We certainly don't use antidepressants based upon mg/kg oral dosing schedules.”

subjects, with five receiving the MDMA and two the placebo, making the chance of receiving the MDMA (71%) larger than the odds of receiving the placebo (29%). The fifth subgroup, receiving the highest dose (150 mgs), will include only four subjects, with three receiving the MDMA and one receiving the placebo.

A study designed with a larger percentage of the subjects receiving the MDMA than the placebo will still be sufficient to introduce an element of uncertainty into whether the placebo or MDMA will be administered. The unequal allocation of a larger number of subjects to MDMA than to placebo permits more data about the effects of MDMA to be gathered from the same size pool of subjects than would equal allocation, which would result in fewer subjects receiving MDMA. In addition, the disproportionate allocation to MDMA is sensitive to the desires of the subjects to receive MDMA instead of placebo, since they can expect to benefit little from being administered the placebo but might benefit from receiving the MDMA. The use of unequal allocation to treatment or placebo groups is supported by the International Conference on Harmonization (ICH) guidelines. ICH Guidelines state, “In any placebo-controlled study, unbalanced randomization (e.g. 2:1, study drug to placebo) may enhance the safety data base and may also make the study more attractive to patients and/or investigators.”<sup>1183</sup>

In order to evaluate the effectiveness of this approach in achieving a double-blind, the subjects as well as the members of the experimental team will record their guesses about whether the placebo or the MDMA was administered. Due to the unequal allocation of placebo subjects to MDMA subjects in each group, this design is more likely to achieve a single blind than a double blind. Subjects will not be told anything about whether previous subjects in their group received either the MDMA or the placebo. In the medium-dose groups, where it is somewhat easier for both subjects and experimenters to distinguish between the MDMA and placebo, the members of the research team will probably be aware of how many subjects had already been randomly allocated to the placebo. The experimental team will be able to use that information to improve the accuracy of their guesses about whether subsequent subjects are administered either MDMA or placebo. In the high-dose groups, it is likely that everyone will be able to tell whether the subjects had been administered MDMA or placebo.

Though this study will use an inactive placebo, an active placebo could theoretically have been chosen. An inactive placebo can be effective in creating a successful double-blind experiment when very low doses of the test drug are used, but usually fails to do so at higher dose levels. An active placebo would probably be more effective than an inactive placebo in creating uncertainty in the minds of subjects who had no prior experience with MDMA about whether they were administered the MDMA or placebo, but would still be of limited effectiveness.<sup>1184</sup> The major complication with the use of an active placebo is that this

<sup>1183</sup>ICH Draft Consensus Guideline, Choice of Control Group in Clinical Trials, Section 2.1.5.2.5. Other Design Considerations.

<sup>1184</sup>In subjects with prior experience with MDMA, the use of active placebo is likely to be ineffective in

study is in psychologically vulnerable patients. To the extent that the active placebo does possess a certain side effect profile without at the same time offering any potential therapeutic benefits, patients who are randomized to the active placebo receive no benefits and some possibility of a minimal degree of discomfort. Jose Carlos Bouso reported, “I decided to use an inactive placebo because there is no evidence that amphetamine [one possible active placebo] benefits patients with PTSD. For me, the first thing is the safety of the subjects. What reason is there to give amphetamine to subjects without a history of drug use if they will not obtain any benefit?”<sup>1185</sup>

An important therapeutic argument against the use of an active placebo is that all subjects will be encouraged to explore psychologically difficult and painful emotions related to their original traumatic event. This exploration requires a certain amount of courage and trust. If patients knew that they could be given an active placebo instead of MDMA, the uncertainty that they would feel when subjective changes started to manifest might cause them to hold back on entering challenging emotional territory. They could hesitate out of concern that if they had been administered an active placebo instead of the MDMA, it would not provide the psychological assistance that might be possible with MDMA. This could compromise the therapeutic effectiveness of the MDMA and have a counter-productive effect. Given the sensitivity to the need to do no harm to placebo patients and the desire to maximize the effectiveness of the therapeutic potential of MDMA, the use of an active placebo in patient populations should be considered when such methodologies are the only way to gather necessary information. Since an inactive placebo can also suffice as a control condition in this initial dose-escalation study, the use of an active placebo is unwarranted.

In preliminary dose-escalation studies in patient populations, the randomization of patients in need of treatment to placebo group, either active or inactive, can be criticized on ethical grounds where accepted treatments with proven efficacy are available. In this study, however, the inclusion criteria require that subjects have previously failed on at least one prior course of treatment. The use of patients who are non-responsive to treatment reduces the ethical concern about the use of placebos as well as unproven new treatments such as MDMA itself which has a level of risk that seems minimal but is not completely known.

The ethical concern about the use of placebos in a patient population is not eliminated

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most subjects. In the Phase 1 dose-escalation safety study conducted in Spain, eight subjects with prior experience with the recreational use of MDMA were administered on four separate occasions at least a week apart either 75 mgs of MDMA, 125 mgs of MDMA., 40 mgs of amphetamine, or inactive placebo. Even when a relatively low dose of 75 mgs of MDMA was used, almost all subjects were able to distinguish between MDMA, amphetamine and inactive placebo. The researchers reported that “Amphetamine was correctly identified by all but two subjects, and one subject identified MDMA 125 as amphetamine.” Mas M, Farre M, de la Torre R, Roset PN, Ortuno J, Segura J, Cami J. Cardiovascular and neuroendocrine effects and pharmacokinetics of 3, 4-methylenedioxymethamphetamine in humans. *J Pharmacol Exp Ther* 290 (Jul 199) 1:136-45.

<sup>1185</sup>personal communication, Jose Carlos Bouso, April 7, 2000.

entirely by requiring subjects to have failed to obtain relief from at least one standard treatment, since there are numerous psychotherapeutic approaches to the treatment of PTSD, each with varying degrees of research supporting claims of efficacy. However, as noted in the protocol, “There does not seem to be much difference between the effectiveness of the various approaches... Research into PTSD in victims of sexual assault is still in its infancy. There are few studies with rigorous controls that demonstrate the effectiveness of one psychotherapeutic approach over another, not only in victims of sexual assault, but in PTSD sufferers in general. Therefore, more well-designed studies comparing the effectiveness of the psychotherapeutic techniques presently available are needed before we can decide which is best for this type of patient.”<sup>1186 1187</sup>

There is only one FDA-approved pharmacological treatment for PTSD, Zoloft, approved on December 7, 1999.<sup>1188</sup> Zoloft has not yet been approved for PTSD in Spain, but it is available by prescription for other indications and could be prescribed for PTSD.

The key ethical issue is not whether patients have failed to find relief with all alternative treatments but whether patients can voluntarily give informed consent to participate in a study in which they might not receive any treatment for a limited period of time. The period of time that subjects are asked not to seek other treatments is quite short, only 30 days prior to their single treatment session. Subjects can seek out other treatments at any time after their treatment session. As previously discussed in this chapter, Dr. Temple and others have made strong ethical arguments supporting the rights of patients to give informed consent to the possibility of experiencing discomfort resulting from the lack of symptomatic relief, even when treatments with some degree of efficacy are already available for those symptoms.

In this study, stop rules have been decided upon ahead of time for the most likely adverse effects, calling for the study to be halted if any subject experiences a cardiovascular crisis or persisting adverse psychological consequences stemming from the experimental session. Prompt treatment will be administered in the event of any adverse event. If the study is stopped, all the data are analyzed and the study cannot begin again unless both the Spanish Ministry of Health and the appropriate Institutional Review Board (IRB) decide to

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<sup>1186</sup>Spanish Drug Agency Code Protocol # 99-0309 Administration of 3,4 Methylendioxy-methamphetamine (MDMA) to Women with Chronic Post Traumatic Stress Disorder (PTSD) as a Consequence of Sexual Assault. A Dose-Finding Pilot Study. 32.

<sup>1187</sup>In the 10/8/1999 FDA Psychopharmacologic Drugs Advisory Committee meeting held to discuss the research with Zoloft in the treatment of PTSD, Dr. Charles Marmar, Professor and Vice-Chair, Department of Psychiatry, UC San Francisco, reported that “the total N of all patients enrolled in randomized controlled trials in the world published literature to date, including those assigned to the placebo condition, is only slightly over 400.” Transcript, FDA Psychopharmacologic Drugs Advisory Committee Meeting 10/8/1999, 29. <http://www.fda.gov/ohrms/dockets/ac/cder99t.htm#Psychopharmacologic%20Drugs>.

<sup>1188</sup>FDA Drug Approvals List for December 1999. <http://www.fda.gov/cder/da/da1299.htm> Also see: FDA Talk Paper T99-55 FDA Approves Zoloft for PostTraumatic Stress Disorder December 7, 1999.

permit the study to resume, perhaps with additional safeguards such as refined exclusion criteria or closer monitoring for possible adverse effects.

### Phase III Treatment Studies: High-Dose v. Low Dose

In the last twenty-five years, there have been only two controlled studies of the therapeutic use of any psychedelic drug conducted anywhere in the world. Both of these studies were conducted by Dr. Evgeny Krupitsky, St. Petersburg (Russia) Scientific Research Center for Addictions and Psychopharmacology. Dr. Krupitsky's initial study evaluated the use of ketamine-assisted psychotherapy in the treatment of alcoholics.<sup>1189</sup> His subsequent study evaluated the use of ketamine-assisted psychotherapy in the treatment of heroin addicts.<sup>1190</sup>

Dr. Krupitsky's study in alcoholics showed a remarkable treatment effect. He reported, "The results of our controlled clinical trial demonstrated a considerable increase in efficacy of our standard alcoholism treatment when supplemented by ketamine psychedelic therapy (KPT): a total abstinence for more than one year was observed in 73 out of 111 (65.8%) alcoholic patients of the KPT group, compared to 24% (24 out of 100 patients) of the conventional treatment control group ( $p < 0.01$ )."<sup>1191</sup> However, a serious methodological flaw in the design of this study makes it difficult to attribute the increased rate of abstinence in the ketamine treatment group to the ketamine treatment alone. At the end of the standard course of in-patient treatment, all patients were asked whether they wanted to volunteer for ketamine treatment. The ketamine group was composed of those patients who volunteered, the control group was composed of those who did not volunteer for the additional ketamine treatment but received only the standard treatment. This procedure introduced a selection bias into the study, since the subjects who volunteered for the ketamine treatment may have been more highly motivated toward sobriety than those patients who did not volunteer for this additional treatment.

This methodological flaw was corrected in Dr. Krupitsky's study with heroin addicts, which was conducted in a randomized, double-blind, placebo-controlled manner.<sup>1192</sup> At the completion of the standard in-patient treatment program for heroin addiction, patients were asked to volunteer for an experimental treatment with ketamine. Subjects who volunteered were then randomized into one of two treatment groups, a high-dose ketamine treatment group or a control group receiving a low dose of ketamine as an active placebo. Dr. Krupitsky improved the protocol design in another way by instituting the measurement of abstinence through the use of frequent though non-random urine tests in addition to reports from the patients themselves, their families and their employers, as

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<sup>1189</sup>Krupitsky (1999).

<sup>1190</sup>Krupitsky (1997).

<sup>1191</sup>Ibid., 165.

<sup>1192</sup>Krupitsky E. Ketamine Psychedelic Therapy in the Treatment of Heroin Addiction v04 Research Protocol <http://www.maps.org/research/ketamine/04Kheroin.html>

well as information about the subjects' interactions with the Russian health care and criminal justice systems.<sup>1193</sup> Follow-up data were collected by psychiatrists who were blind to the dose of ketamine used for KPT.

Dr. Krupitsky's choice of a low dose of ketamine as an active control was based on his view that patients could easily distinguish between a high dose of ketamine and either an inactive placebo or any active placebo. In order to come as close as possible to a truly effective double-blind study, or at least a single-blind, Dr. Krupitsky decided to use as an active control a low dose of the same psychedelic being tested. This strategy is consistent with ICH guidelines, which encourage the use of dose-response designs when the effects of the drug make blinding difficult. ICH Guidelines state, "If the dose-response study is blinded, it shares with other blinded designs an ability to minimize subject and experimenter bias. When a drug has pharmacologic effects that could break the blind for some patients or investigators, it may be easier to preserve blinding in a dose-response study than in a placebo-controlled trial."<sup>1194</sup>

Dr. Krupitsky's strategy to achieve a double-blind study worked in part. Subjects were not able to determine whether they had received a high or a low dose, but the experimental team was able to make this determination in about 90% of the cases.<sup>1195</sup> The disadvantage of using the low-dose ketamine session as the placebo control condition was that the low dose was large enough to catalyze some psychological processing, enabling the low-dose ketamine session to have some therapeutic effects.<sup>1196</sup> This was confirmed by subjects' scores on the Hallucinogen Rating Scale (HRS), developed by Dr. Strassman to measure a range of effects of psychedelic drugs.<sup>1197</sup> Dr. Krupitsky reported, "The results of this double-blind randomized clinical trial of KPT for heroin addiction showed that high dose (2.5 mg/kg) ketamine psychedelic psychotherapy (KPT) elicits a profound, full psychedelic experience in heroin addicts. On the other hand, low dose KPT (0.25 mg/kg) elicits "sub-psychedelic" experiences which are very similar to ketamine-facilitated guided imagery... Patients in the control group were often very much impressed by their experiences and considered them as useful and therapeutic ones."<sup>1198</sup>

<sup>1193</sup>Dr. Krupitsky is planning to submit his findings for publication to a major international drug abuse treatment journal by the end of Summer, 2000, at which time two-year follow-up data will have been gathered on all subjects.

<sup>1194</sup>ICH Draft Consensus Guideline, Choice of Control Group in Clinical Trials. Section 2.3.2 Ability to minimize Bias.

<sup>1195</sup>personal communication, Dr. Krupitsky, March 10, 1999.

<sup>1196</sup>Krupitsky (1999): 24.

<sup>1197</sup>Strassman R. Subjective effects of DMT and the development of the Hallucinogen Rating Scale. *Bull MAPS* 3 (Spring 1992) 2:8-12. <http://www.maps.org/news-letters/v03n2/03208dmt.html>

<sup>1198</sup>Krupitsky (1999): 24.

It would have been easier for Dr. Krupitsky to find a statistically significant treatment difference between a high dose and an inactive placebo.<sup>1199</sup> When a low-dose/placebo condition has some marginal efficacy, it becomes more difficult to find a statistically significant treatment difference between a high-dose experimental condition and a low-dose/placebo. However, if a treatment effect can be shown under such conditions, it can be considered robust. Larger sample sizes can help counteract the statistical difficulties created when a low-dose/placebo turns out in practice to have some degree of efficacy, but that is an expensive remedy.<sup>1200</sup>

Despite difficulties stemming from the use of a control condition with some degree of efficacy, Dr. Krupitsky reported that, “The rate of abstinence in the experimental (high dose) group was approximately twice as high as that of the control (low dose) group...<sup>1201</sup> KPT with the high-dose of ketamine was significantly more effective [than KPT with the low-dose of ketamine] within the first six months after the ketamine session.”<sup>1202</sup>

Dr. Krupitsky’s initial study in heroin addicts demonstrated the effectiveness of a single high-dose treatment session over a single low-dose treatment session. Though it is reasonable to assume that a low-dose ketamine session would produce a greater rate of sobriety than a psychotherapy-only treatment without the ketamine, Dr. Krupitsky’s study design can be criticized for the lack of just such a control group. In the absence of the evaluation of the effectiveness of a parallel group receiving psychotherapy alone, it is doubtful whether FDA would consider this design to be an “adequate and well-controlled investigation” proving the effectiveness of ketamine-assisted psychotherapy in heroin addicts.<sup>1203</sup>

### Phase III Treatment Study: Single Dose v. Multiple Dose

Dr. Krupitsky has recently initiated a new study in heroin addicts designed to evaluate the effectiveness of single versus multiple KPT sessions. Specifically, he will

<sup>1199</sup>In a review that evaluated the use of an active placebo in studies of the effectiveness of tricyclics for depression., it was found that comparing the active drug to the active placebo resulted in a lower estimate of the effectiveness of the active drug than when the active drug was compared to placebo. Thompson R. Side Effects and placebo amplification. *Br J Psychiat*140 (1982): 64-68.

<sup>1200</sup>ICH Draft Consensus Guideline, Choice of Control Group in Clinical Trials. Section 2.1.6.3 Efficiency, states, “Placebo-controlled trials are efficient in that they can detect treatment effects with a smaller sample size than any other type of concurrently controlled study.”

<sup>1201</sup>The rate of abstinence was calculated as a ratio of the number of subjects who were abstinent at every time point that follow-up data was collected (one month, two months, three months, etc.) to the total number of patients in the group.

<sup>1202</sup>Krupitsky (1999): 24.

<sup>1203</sup>Of course, FDA might also have concerns about other aspects of the study such as sample size and the extent of independent clinical monitoring that is often required in the primary studies used to demonstrate safety and efficacy.

compare the efficacy of a single high-dose ketamine session followed by two additional non-drug counselling sessions to three high-dose ketamine sessions. All treatment sessions will be scheduled about four weeks apart. The inclusion of the two counseling sessions for the single dose group is intended to equalize the time patients spend with their therapists. The counseling sessions can be considered psychotherapy-only sessions.

There is no active or inactive placebo group or low-dose group in the current study. According to Dr. Krupitsky, the addition of such groups would not have been useful in evaluating the central hypothesis of the study, whether multiple sessions are more effective than a single session. Nor did he think it necessary to show that both treatments were more effective than an inactive or active placebo condition, since he had already successfully demonstrated that his treatment intervention was more effective than low-dose ketamine in his previous study. Dr. Krupitsky felt confident that his findings of treatment efficacy for the high-dose session were robust, and didn't need to be proven again at substantial expense.<sup>1204</sup>

One possible criticism of Dr. Krupitsky's decision not to include another control group in the study of a single session compared to multiple sessions comes from arguments expressed by FDA's Dr. Temple. He has pointed out that the lack of a control group in studies comparing two active treatments means that "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."<sup>1205</sup> This argument raises an ethical issue. Dr. Temple qualified his remedy as being for the symptomatic treatment case, for a study treating symptoms that are not in and of themselves fatal, and do not lead to increased mortality if untreated. However, heroin addiction is a disease that is potentially fatal. Every addict has a non-zero, empirically determined risk of addiction-related mortality if the underlying addiction goes untreated. According to Dr. Krupitsky, "I do not know the exact mortality rate for heroin addicts in Russia, but it is quite high (much higher than in the general population). Heroin addicts die from overdoses, hepatitis B and C, crime and HIV (the HIV epidemic is just starting to develop in Russia)."<sup>1206</sup> As a result of the potentially fatal consequences associated with their underlying addiction, it could be considered unethical to ask a subject to participate in a placebo-controlled trial when there is already a proven treatment (the single high-dose session) that has a greater chance of being effective than either an inactive placebo or the low-dose, active placebo treatment. Furthermore, due to the dramatic nature of the ketamine experience, the placebo condition would not actually succeed in producing a successful

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<sup>1204</sup>personal communication, Dr. Krupitsky, February 4, 2000.

<sup>1205</sup>Temple (1997): 617.

<sup>1206</sup>personal communication, Dr. Krupitsky, March 12, 2000.

double-blind or even single-blind experiment.

Dr. Krupitsky's decision not to include a psychotherapy-only or low-dose treatment group or groups is substantially influenced by another factor; ketamine is already an approved prescription drug in Russia. As a result, Dr. Krupitsky does not need to convince any regulatory agency to make ketamine available as a prescription drug. Ketamine is already available for prescription for his therapeutic practice and research as well as for the original purpose for which it has been approved, as an anesthetic for use in medical operations. If other physicians involved in treating substance abuse patients are impressed with Dr. Krupitsky's experimental results, they may administer ketamine-assisted psychotherapy to their patients within the boundaries of the legal practice of medicine.<sup>1207</sup> Dr. Krupitsky's current design thus seems sufficient as is for his purposes, even though FDA might not consider it an "adequate and well-controlled investigation" capable of providing evidence for the approval in the United States of ketamine-assisted psychotherapy in the treatment of heroin addiction.

As the study is now designed, subjects will be randomized to the single-dose group or to the multiple-dose group several days before the second treatment session, when the experimental staff contacts the patient to schedule the second treatment session. This is close to the last possible moment the randomization could have taken place, immediately prior to the second treatment session. The randomization is being done several days prior to the second session so that subjects can come prepared for the type of session they will actually receive. Otherwise, all subjects would have had to come prepared for a ketamine session, including for some the bringing of a friend or relative to assist in their readjustment to their normal state of consciousness in the hours after their KPT session.

Dr. Krupitsky had initially intended to break the blind at the beginning of the study, instead of a few days before the second treatment session. His rationale was that, "I believe that for the treatments to be most effective, the subjects of the single KPT group should be psychotherapeutically prepared, should have a special set, special attitude already before their only KPT session. They should be ready to try to solve their psychological problems, to accept new life values and purposes, a new meaning of life without heroin within one KPT session followed by two counseling sessions. For the psychotherapy to be most successful in the multiple KPT group, the patients of that group should have another set at the very beginning: to do all things mentioned above within three KPT sessions where each next session is a consecutive stage in this process."<sup>1208</sup>

While Dr. Krupitsky had a solid rationale for preparing each patient as effectively as he thought possible for the treatments they would actually receive, there were methodological costs associated with breaking the blind before it was absolutely necessary by the nature of the protocol design. The possibility could not be eliminated that right from

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<sup>1207</sup>The ability of physicians to prescribe already approved drugs for indications other than the approved indications will be discussed in more detail in Chapter 5.

<sup>1208</sup>personal communication, Dr. Krupitsky, April 15, 2000.

the beginning of the study unconscious or conscious bias would influence the perceptions of the subjects and the experimental team about the different chances for sobriety of the subjects in the two different groups. Dr. Lasagna emphasizes that, “the extent to which physicians and patients approach a given treatment with either positive or negative bias can add to or subtract from the ‘intrinsic’ performance of the drug.”<sup>1209</sup> Breaking the blind at the beginning of the study might have increased the influence of such bias, even though this bias would inevitably come into play to some extent, since the blind cannot be sustained beyond the moment the second session begins, when patients are either administered KPT or a counselling session. Dr. Laska et al. comment, “As an abiding principle, RCTs [ randomized controlled trials] designed for hypothesis testing should strive for the most rigorous blinding procedures possible in order to minimize the risk of compromising the study’s integrity, which inevitably leads to uncertainties about the validity of inferences.”  
1210

Another potential problem with Dr. Krupitsky’s initial preference to break the blind at the beginning of the study was the possibility that his results might be biased by differential drop-out rates. These rates may differ between the subjects who know they are randomized to receive all three ketamine sessions and the subjects who instead know they are randomized to receive just one ketamine session and two non-drug “placebo” counselling sessions. As Dr. Krupitsky reported in his article on the high-dose versus low-dose study, “It is important to note that almost 50% of patients in the experimental group and 60% of subjects in the control group relapsed within the first three months after KPT.”<sup>1211</sup> A greater number of subjects who are randomized to receive the single KPT session followed by the two counseling sessions may not show up for their second session since they know they have no possibility of receiving another KPT session.

Regardless of when the blind is broken, if the multiple KPT sessions really do have additive therapeutic effects, it is possible that more of the single KPT subjects will relapse after the second and before the third sessions, at a higher rate than the subjects randomized to receive three ketamine sessions. On the other hand, the KPT sessions are not generally considered pleasant, so some less motivated subjects in the multiple dose group might choose to stay away from the intensive self-confrontation they could expect in their second and third sessions. As Dr. Laska et al. note, “Excessive dropouts, especially early in treatment, can seriously impair the validity of an RCT and limit inferences that can be drawn from the results.”<sup>1212</sup> After considering all the arguments for when to break the blind, Dr. Krupitsky decided to sustain the blind for as long as possible, breaking it only several days before the second session.

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<sup>1209</sup>Lasagna (1994): 27.

<sup>1210</sup>Laska et al. (1994): 60.

<sup>1211</sup>Krupitsky (1999): 24.

<sup>1212</sup>Laska E et al. (1994): 60.

Subjects who do not complete all three sessions will be replaced in the study with new subjects who do complete all three sessions. Those subjects who complete the full course of one high-dose ketamine session and two counseling sessions might be more motivated than average to achieve sobriety, either right from the beginning of the study or because of a more successful than average initial ketamine session. If there is a differential attrition rate of the subjects in the control group who are less motivated to sobriety than average, the results for the control group could be biased. An increased rate of sobriety due to the greater motivation of the subjects who remain in the study for their one KPT session and two counseling sessions would instead be attributed to the effects of the control treatment. The effect of this selection bias would be to make it more difficult to demonstrate a significant treatment effect of the multiple ketamine sessions over the single ketamine session. This bias, if it really occurs, would ensure the robustness of any findings of a significantly improved rate of sobriety between subjects receiving multiple ketamine sessions as compared to those receiving a single ketamine session. A second analysis of the data from an intent-to-treat perspective, in which data from all subjects initially enrolled in both groups is included with drop-outs considered to have relapsed, would help identify whether differential drop-out rates are actually a factor biasing the results.<sup>1213</sup>

#### Phase III Efficacy Studies: Dose-Response Designs

As proposed in Chapter 4, psychedelic psychotherapy can be adequately evaluated through the use of a two-arm study, one arm being a group receiving psychedelic psychotherapy with a full dose of the psychedelic drug and the comparison control group receiving the identical psychotherapy without a psychedelic. Though this design is not blinded, the efficacy of these two groups can still be sufficiently compared. As noted in the introduction to this chapter, an adequate evaluation of psychedelic psychotherapy may not be a politically sufficient evaluation. It may be necessary to add additional controls to the two-arm design to make any findings of efficacy more robust and incontrovertible. The main design element missing in the two-arm study as currently proposed is the lack of a double-blind between the two test groups.

As discussed throughout this chapter, the combination of the powerful subjective effects of a full dose of a psychedelic drug along with even the minimal information contained in an informed consent form ensure that most or all subjects would be able to distinguish a full dose of the test drug from inactive or active placebo. In addition, experienced therapists would be able to use their knowledge of the subjective effects of fully therapeutic doses to determine in most or all cases whether their patients had been administered the test drug or an inactive or active placebo.

The most appropriate method to address this problem is the use of a dose-response

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<sup>1213</sup>For a discussion of issues relevant to intent-to-treat (ITT) analysis, see Lavori P, Laska E, Uhlenhuth E. Statistical Issues for the Clinical Evaluation of Psychotropic Drugs. in (ed.) Prien R, Robinson D. *Clinical Evaluation of Psychotropic Drugs: Principles and Guidelines*. New York: Raven Press, 1994.139-160.

study. Indeed, the ICH guidelines make the following recommendation, “When a drug has pharmacologic effects that could break the blind for some patients or investigators, it may be easier to preserve blinding in a dose-response study than in a placebo-controlled trial.”<sup>1214</sup> According to Dr. Lyons of the Irish Medicine Board, “demonstration of a dose-response effect can also offer persuasive evidence of effectiveness.”<sup>1215</sup> Dr. Lasagna concurs, explaining that, “If a dose-response relationship can be demonstrated in an experiment, the need for placebos is considerably lessened, but this means the trial must be run as a fixed-dose design.”<sup>1216</sup>

The current two-arm study could be expanded into a dose-response study with the addition of a third test group receiving psychedelic psychotherapy with a medium-size dose of the psychedelic drug. These doses can be those determined in prior Phase II dose-escalation studies. The medium dose would be selected to be well above the threshold for generating the unique psychedelic changes catalyzed by the test drug but would be a smaller dose than that used in the group receiving a fully-active dose. The inclusion of both a medium-dose and a fully-active dose would provide the necessary minimum of two points in a dose-response relationship. The use of both medium-size doses and fully-active doses would stand the best chance of blinding a substantial number of subjects and members of the experimental team as to which doses the subjects had actually received.

In addressing the issue of blinding, the medium-size dose also has ethical advantages. Since the dose would be chosen to have a significant psychedelic effect, there would be no ethical concerns associated with randomizing patients in need of treatment to this group. The medium-size dose group would clearly be hypothesized to be more effective than a low-dose group as well as the psychotherapy-only control group. As noted previously, one of the advantages of the psychotherapy-only control group is that it is hypothesized to have more efficacy than an inactive placebo control group, since the psychotherapy-only control group would offer subjects clinical benefits associated with its psychotherapeutic components.

The two-arm study proposed in Chapter 4 has now been enlarged to a three-arm study. The inclusion of a control group receiving the identical preparation and therapy as the high-dose and medium-dose groups but without the addition of the psychedelic drug provides a method to evaluate the contribution of the psychotherapy alone as well as differing amounts of the psychedelic drug.<sup>1217</sup> The inclusion of a psychotherapy-only group also provides the advantage of eliminating the need to rely on a comparison of the two active treatments to historical controls.

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<sup>1214</sup>ICH Draft Consensus Guideline, Choice of Control Group in Clinical Trials. Section 2.3.2 Ability to minimize Bias.

<sup>1215</sup>Lyons (1999:): 263.

<sup>1216</sup>Lasagna (1994): 26-27.

<sup>1217</sup>For details on how this might be accomplished with precision, see: Hollon et al. (1991).

### Phase III Efficacy Studies: Psychotherapy-Only Control with Sub-Threshold Dose

It may be possible to further improve upon the design of the three-arm study proposed above through the administration to the subjects in the psychotherapy-only condition of a sub-threshold dose of the psychedelic drug being tested. This is somewhat similar to the precedent established by FDA when it reviewed the psilocybin/OCD dose-response study to be conducted by Dr. Moreno and Dr. Delgado. In that study, FDA recommended the use of a sub-threshold or barely-threshold dose of psilocybin as a control condition instead of an inactive or active placebo.

In the psychotherapy-only group, the sub-threshold dose would be chosen to be well below the level of detection so as not to confound the psychotherapy-only condition with any pharmacological effects. The inclusion of a sub-threshold dose in the psychotherapy-only group would maximize the placebo effect in the psychotherapy-only subjects, more so than would the use of either an inactive or active placebo. The use of a sub-threshold dose of the test drug would make all subjects and experimenters aware that every subject would receive some amount of the test drug. This would increase the possibility of a placebo reaction in those subjects receiving the sub-threshold dose, perhaps increasing the chances that some subjects would catalyze a psychological reaction through expectation and be blinded as to whether they were in the psychotherapy-only group or the medium-dose group. More likely than actually blinding subjects, the use of a sub-threshold dose might simply increase the sense of possibility that all subjects and experimenters brought to every session.

It is likely that most or all subjects receiving the sub-threshold dose would notice an absence of psychedelic effects and would be able to identify that they had been administered the lowest dose of the test substance. The ability to break the blind would be somewhat more likely if an inactive placebo had been administered, since there would be no expectation of subtle effects from the sub-threshold dose. Another advantage of the administration of a sub-threshold dose is that it would provide one more point on the dose-response curve while not confounding the psychotherapy-only group with any appreciable pharmacological contribution to the treatment.

The use of an active placebo instead of the sub-threshold dose of the psychedelic in the psychotherapy-only group might make it difficult for a few subjects and experimenters to distinguish between the active placebo and the medium dose of the psychedelic. However, an active placebo would fail in most or all instances to create such uncertainty in relation to the high dose, which hypothetically has the greatest therapeutic potential and is the most important condition being compared to placebo. A serious disadvantage from the use of an active placebo with some side effect profile and no potential therapeutic benefits in vulnerable patient populations is that it is questionable ethically, especially when the ability of the active placebo to achieve either a single or double blind is so limited. Most

importantly, an active placebo above the threshold for detection changes the psychotherapy-only control and could bias the outcome of the psychotherapy-only condition in unpredictable ways. As Dr. Lasagna observes, “it is not always possible to guarantee a priori that the drug or drugs placed in the active placebo will be free of beneficial or deleterious effect on the parameters under study.”<sup>1218</sup>

Drs. Hollon and DeRubeis express a preference for a psychotherapy-only condition that does not involve any placebo, either a sub-threshold dose of the psychedelic, an active placebo or an inactive placebo. They remark, “Such a procedure is seen in this article as unjustifiable. These combinations involve potential additive or interactive effects derived from the patient’s or the therapist’s perceptions that the patient is receiving an active medication. This perception renders this condition non-representative of psychotherapy as it is typically practiced.”<sup>1219</sup> They note that the use of a placebo in the psychotherapy-only condition makes it impossible “to determine whether psychologically mediated effects related to pill taking did or did not occur...The placebo-plus-psychotherapy combination, though useful in determining the nature of the mechanisms in interaction effects, does not provide an adequate basis for detecting differential outcome.”<sup>1220</sup> Drs. Hollon and DeRubeis further claim that in some circumstances, the combination of psychotherapy even with an inactive placebo could be less effective than psychotherapy alone. They noted that, “a review of the existing drug-psychotherapy literature points to bidirectionality in the noncomparability of placebo plus psychotherapy relative to psychotherapy alone. That is, the combination may sometimes overestimate, but appears more typically to underestimate, the efficacy of psychotherapy alone... Although it would be inappropriate to conclude at this time that negative placebo-plus-psychotherapy interactions occur, it would also clearly be unwarranted to assume, as has been the case, that they do not.”<sup>1221</sup>

In considering the arguments of Drs. Hollon and DeRubeis, it must be kept in mind that they are reviewing studies in which the psychotherapy takes place in small increments over many weeks. This pattern of interactions is substantially different from the psychotherapy-only condition, which involves a preparation phase combined with a lengthy acute intervention phase and then an integrative phase. In addition, the placebo used in these studies is taken every day for the duration of the study, just like other psychiatric medications, and is likely to be somewhat more effective on average than the sub-threshold dose in actually blinding the subjects and experimenters. Drs. Hollon and DeRubeis speculate that possible mechanisms for an enhanced effect from the use of the placebo are “positive treatment expectations and response to perceived attention from a physician.”<sup>1222</sup>

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<sup>1218</sup> Lasagna (1994): 26.

<sup>1219</sup> Hollon S, DeRubeis R. Placebo-Psychotherapy Combinations: Inappropriate Representations of Psychotherapy in Drug-Psychotherapy Comparative Trials. *Psychologic Bull*90 (1981) 3:467.

<sup>1220</sup> Hollon, DeRubeis (1981): 468.

<sup>1221</sup> Hollon, DeRubeis (1981): 473.

The possible mechanisms for a negative interaction between placebo and psychotherapy are “reduced motivation to work actively in psychotherapy and the decay of positive treatment expectations over time.”<sup>1223</sup>

In the psychotherapy-only group, the sub-threshold dose might indeed generate some positive treatment expectations, at least for some portion of the treatment session. This is the main reason for the recommendation that a sub-threshold dose be administered instead of no placebo at all. In the studies that Drs. Hollon and DeRubeis review, the subjects receive psychotherapy delivered by psychotherapists and would receive extra attention from a physician, who would administer the placebo pill. In the psychotherapy-only group in the psychedelic study, no additional treatment providers would administer the pill. It would be administered by the same therapeutic team that would administer the psychotherapy-only condition, eliminating this potential positive interaction. There is a possible negative interaction from a reduced motivation to work actively in psychotherapy as a result of the subject deciding to let the pharmacological treatment do more of the work. This could be a factor in a study of traditional pharmacotherapy and psychotherapy. With a sub-threshold dose of a psychedelic instead of no drug at all, subjects would probably be more motivated to explore their emotions during the psychedelic treatment session rather than less. The hypothesis of Drs. Hollon and DeRubeis is that the decay of positive expectations over time could negatively interact with psychotherapy. Their hypothesis is based on the declining placebo effect over time, though they admit that there is no evidence that any negative interaction would be caused. Again, this factor is more relevant for a traditional psychotherapy/pharmacotherapy study than for an acute psychotherapeutic intervention with a sub-threshold dose of a psychedelic.

On balance, a sub-threshold dose of a psychedelic seems most likely to interact positively with psychotherapy through positive treatment expectations. If anything, this could increase the efficacy of the psychotherapy-only condition, thus making it somewhat more difficult to show a significant treatment effect between the psychotherapy-only condition and the medium and high-dose treatments. The contribution of the sub-threshold dose to maximizing the placebo effect, and the ability to plot a third point in the dose-response relationship, are the principal benefits of combining the psychotherapy condition with a sub-threshold dose.

#### Unequal Allocation to Psychotherapy-Only Control Group

The three-arm study design may be further improved through the use of an unequal allocation of subjects to the psychotherapy-only condition with the sub-threshold dose, as compared to the medium-dose and high-dose groups. Such unequal allocation would ensure a larger number of subjects in the two treatment groups that are hypothesized to have greater efficacy than the psychotherapy-only condition with the sub-threshold dose. This unequal allocation would further improve the ethical aspects of this study by providing more

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<sup>1222</sup>Hollon, DeRubeis (1981): 475.

<sup>1223</sup>Hollon, DeRubeis (1981): 475.

patients with what is hypothesized to be more effective treatment.

The number of subjects that remain allocated to the psychotherapy-only condition with sub-threshold dose needs to be sufficient not to compromise the ability of that group to serve as the primary control group for the two active conditions. Though the exact numbers will need to be determined by the power calculations, a desirable outcome might be to have half as many subjects in the psychotherapy-only condition with sub-threshold dose as are in the other two arms of the study. Dr. Lieberman et al. elaborate, “Several strategies have been used to address the dual problems of need for control and need to minimize placebo exposure. One such strategy is unequal randomization. If a sample is large enough and the placebo response rate is fairly well known, a study can be conducted with only a small placebo group.”<sup>1224</sup>

### Phase III Efficacy Studies: Comparison To Currently Accepted Treatment

There is one fundamental enhancement remaining to consider for Phase III efficacy trials designed to evaluate psychedelic psychotherapy, an enhancement that will make the studies scientifically adequate and politically responsive. A three-arm study with a psychotherapy control group receiving a sub-threshold dose, a medium-dose group and a high-dose group would generate substantial data sufficient for FDA to evaluate psychedelic psychotherapy for possible marketing approval. Yet one important possibility would remain unexamined, that being a comparison study between psychedelic psychotherapy and a currently approved medication or non-drug psychotherapeutic technique for the same clinical indication. Given the level of cultural controversy engendered by psychedelics, it is realistic when considering experimental design issues to consider the potential of political opposition to the socially sanctioned use of psychedelics as prescription medicines. Even if a full-dose psychedelic drug could be proven more effective than a sub-threshold psychotherapy control group, and perhaps also more effective than a medium dose of the same psychedelic, the performance of that drug as compared to currently available medications or psychotherapeutic treatments would still be unclear.

There is no identifiable public health reason for FDA’s standard of proof for the approval of psychedelic psychotherapy to be anything more than the usual comparison against placebo. However, for political reasons a Phase III study should be designed to demonstrate comparability, and perhaps even superiority, to conventional treatment. As Dr. Temple explained about medical marijuana, “Considering the level of controversy and societal expectations, I assume the following factors will influence study design: Unlike most treatments, smoked marijuana may need to show an advantage over alternatives, including tablet THC [more accurately, capsule THC], at least in some defined population, to be considered medically useful by skeptics. NB: Showing superiority to an active treatment is always difficult; study designs need to optimize the chances of showing such an effect.”<sup>1225</sup> Dr. Temple noted that advantages over other medications could be expressed in

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<sup>1224</sup>Lieberman et al. (1999): 31.

terms of superior efficacy in all patients, just in non-responders to other medications or in some other subset of patients including even experienced marijuana smokers, or as an add-on drug that enhances the efficacy of currently available drugs. Advantages could also be expressed in terms of an improved safety profile either in all patients, just in people intolerant of other treatments, or in experienced marijuana smokers. Advantages other than safety and efficacy could include ease of use, more rapid response, or patient preference.<sup>1226</sup> He further advised, "Choose situations where current therapy is not satisfactory, at least for some patients; again any benefit seen will then be clearly worthwhile."<sup>1227</sup>

The inclusion of both the psychotherapy-only and comparison groups together permit a rigorous review of the efficacy of the high-dose condition. If a study were to be designed as a direct comparison of a new and an already accepted treatment, without a parallel control group, then "only when the test treatment is superior to the standard in such a study can the unambiguous interpretation be made that the investigational drug is effective."<sup>1228</sup> Dr. Tom Laughlen, FDA Team Leader in the Division of Neuropharmacological Drug Products, the division that will likely review psychedelic psychotherapy protocols, has commented. "From a regulatory standpoint, we like to see an active control arm in a trial to help us in interpreting it, so that if an active standard drug, which is believed to work, also fails, we are more inclined to discount that study. This is obviously not a strategy you can use early on in the development of a new indication."<sup>1229</sup>

The addition of a fourth arm testing psychedelic psychotherapy against conventional treatment also makes an contribution to the ethics of the use of a design that includes a psychotherapy-only with sub-threshold dose condition. As previously noted, the psychotherapy-only with sub-threshold dose is not actually a placebo condition, but it is hypothesized to be less efficacious than the other two dose levels. As Dr. Lieberman et al. state, "A placebo may also be justifiable when an experimental treatment (T) is being compared to a standard treatment (S). Suppose a trial has only two treatments: T and S. If the trial shows that  $T > S$ , or  $S > T$ , the results are interpretable. But if a two-armed trial compares S and T and fails to find a difference, the result may mean that neither treatment or both treatments were effective. In many cases this ambiguity is avoidable if a placebo group is used."<sup>1230</sup> In these instances, the use of a placebo group increases the interpretability of the information generated from the entire study, adding value to the study thereby reducing

<sup>1225</sup>Dr. Temple, NIH Workshop on the Medical Utility of Marijuana, Slide 5, "Assumptions."

<sup>1226</sup>Dr. Temple, NIH Workshop on the Medical Utility of Marijuana, Slide 7, "Showing Possible Advantages." and Slide 8, "Possible Advantages (Cont'd.)."

<sup>1227</sup>Dr. Temple, NIH Workshop on the Medical Utility of Marijuana, Slide 9, "Choosing Diseases and Endpoints."

<sup>1228</sup>Laska E et al. (1994): 61.

<sup>1229</sup>Transcript of the October 8, 1999 meeting of the Pharmacologic Drugs Advisory Committee: 145.

<sup>1230</sup>Lieberman J et al. (1999): 30.

ethical concerns about randomizing some patients to the placebo group.

### Phase III Efficacy Studies: Impact of Subjects Who are Non-Responders to Treatment

Phase III clinical trials evaluating the efficacy of psychedelic psychotherapy may have inclusion criteria requiring that subjects have previously failed to obtain symptom relief with conventional medications or psychotherapeutic treatments. When patients who have failed on conventional treatment are included in clinical trials, the use of a four-arm study design that includes a comparative group receiving conventional treatment needs to be reevaluated.

The inclusion criteria in the Spain MDMA/PTSD study requires that subjects “have failed at least one previous treatment for resolving the PTSD.”<sup>1231</sup> The psilocybin/OCD protocol states, “Subjects must have failed at least one adequate trial of usual care treatment.”<sup>1232</sup> In a June 24, 1999 discussion concerning Dr. Grob’s proposed study of MDMA in the treatment of cancer patients, FDA’s Dr. McCormick raised the possibility that only non-responders would be permitted to volunteer for the study. She stated that if the primary outcome variable was pain, “The clinical trial should include only subjects who are experiencing non-responsive cancer pain.”<sup>1233</sup> If the primary outcome variable was anxiety, “She [Dr. McCormick] also pointed out that to be eligible, patients would need to have failed standard anxiolytics[anti-anxiety medications].”<sup>1234</sup>

The primary reason that researchers and regulatory agencies decide that clinical trials should only enroll patients who have failed to obtain relief with conventional medications or treatments is that a higher degree of risk is acceptable in this class of patients, whose alternative to the experimental treatment is most likely to be the continuation of the disease process or symptoms. While the risk of the use of psychedelics in clinical research contexts is quite low,<sup>1235</sup> psychedelics are by legal definition drugs with a high potential for abuse,<sup>1236</sup> and regulatory agencies and researchers are reluctant to expose patients to these drugs unless there is a substantial need to do so. An advantage of conducting research with patients who have failed on conventional treatment is that the ethical concern about randomizing subjects in need of treatment to placebo groups would be eliminated, since effective treatment was not being denied. Dr. Lieberman et al. concur, stating that,

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<sup>1231</sup>Spanish Drug Agency Code Protocol # 99-0309 Administration of 3,4 Methylendioxy-methamphetamine (MDMA) to Women with Chronic Post Traumatic Stress Disorder (PTSD) as a Consequence of Sexual Assault. A Dose-Finding Pilot Study. Inclusion Criteria: 55.

<sup>1232</sup>IND # 56,530. Protocol: Effects of Psilocybin in Obsessive-Compulsive Disorder. Inclusion Criteria.

<sup>1233</sup>McCormick C. Letter to Dr. Grob. July 23, 1999: 2.

<sup>1234</sup>McCormick C. Letter to Dr. Grob. July 23, 1999: 2.

<sup>1235</sup>Strassman R. Adverse reactions to psychedelic drugs: A review of the literature. *J Nerv Ment Dis* 172 (1984) 10:577-95.

<sup>1236</sup>Controlled Substances Act of 1970. 91 P.L. 513; 84 Stat. 1236. October 27, 1970.

“Placebos can also justifiably be used for patients who are refractory to standard treatments.”<sup>1237</sup>

The studies mentioned above that require subjects to have failed on conventional treatment are initial pilot studies approved when there were little or no scientific data supporting claims of efficacy and no clear delineation of the actual degree of risk to the specific patient population being tested. If initial pilot studies do find some suggestions of efficacy at acceptable levels of risk, the risk/benefit ratio may change sufficiently so that subsequent clinical trials may not need to be restricted to patients who have failed on conventional medications. Yet it remains possible that subsequent clinical trials may be restricted by regulatory agencies to patients considered treatment failures. For an historical example, Marinol, a capsule containing synthetic THC, the primary psychoactive component of marijuana, was approved by the FDA on May 31, 1985 for the treatment of nausea and vomiting from cancer chemotherapy.<sup>1238</sup> It was studied in patients who failed to find relief with approved medications and is currently labeled for “nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetics.”<sup>1239</sup>

When only subjects who are non-responsive to treatment are included in a four-arm clinical study design that includes a conventional treatment arm, it seems reasonable to assume that these patients will not respond well on average to the conventional treatment. As a result, the new therapy may compare favorably with the conventional treatment due not to any inherent advantage in efficacy of the new treatment but to the use of a sample of patients who are already demonstrated to be non-responders to conventional treatment. A study with a conventional treatment arm could be considered biased if subjects were selected for being non-responsive to conventional treatment.

Dr. Temple has also observed that non-responders to conventional treatment may be more likely on average to show a beneficial effect from new medication. “A non-responder population is ‘enriched’ with patients in whom MJ [marijuana] could be advantageous, and may be better able to show an effect...Non-responders to standard therapy could be studied; more likely to be able to show benefit of a different or added agent.”<sup>1240</sup>

There are several factors that could result in the conventional treatment showing some efficacy even in patients who have previously failed on conventional treatment. There are a variety of conventional treatments, so it is possible that the specific conventional treatment used as a comparative condition may be new to some patients, some fraction of whom may respond well to it. Even if patients receive the same treatment that has previously

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<sup>1237</sup>Lieberman et al. (1999): 30.

<sup>1238</sup><http://www.marinol.com/>

<sup>1239</sup>Arky R. (Medical Consultant). *Physicians Desk Reference, 52nd Edition*. Montvale, NJ: Medical Economics Company. 1998: 2545.

<sup>1240</sup>Dr. Temple, NIH Workshop on the Medical Utility of Marijuana, Slide 7, “General Principles” and Slide 15, “Enrichment.”

failed to help them, factors such as spontaneous remission, maturation out of the disease or symptom, improved coping skills, more effective dosing schedule or treatment delivery, increased placebo effect as a result of being administered the medication or treatment in a clinical trial, or regression to the mean may produce some degree of improvement in these individual patients and in the group average.<sup>1241</sup>

The uncertainty about the effectiveness of a conventional treatment arm even in patients who have previously failed to find relief with conventional treatment makes the inclusion of a comparative control condition desirable even with a treatment-resistant patient population. Though some of the treatment-resistant patients might do well with conventional treatment, it would be likely that they would, on average, show minimal efficacy from a treatment that already failed once. This would increase the chances that the high-dose psychedelic psychotherapy treatment would compare favorably to the conventional treatment group. If only treatment-resistant patients are enrolled in the study, the comparison of most importance would be between psychedelic psychotherapy and the psychotherapy-alone with sub-threshold dose “control” group.

### Selection of Therapists

In a four-arm study comparing psychedelic psychotherapy with a currently available treatment, the therapists delivering the comparative treatment do not need to be the same as those delivering the psychedelic psychotherapy. The therapists delivering each treatment should be proficient in the treatment they are delivering and believe in its potential efficacy. A meta-analysis evaluating 25 different studies comparing the outcomes of two different psychotherapeutic treatments, cognitive therapy or systematic desensitization, or the combination of both, revealed that investigators tend to produce studies that demonstrate the superior efficacy of the treatment they prefer, for which they “had a prior allegiance.”<sup>1242</sup> This suggests that having the same therapists deliver two different treatments could result in a bias in favor of the treatment the therapists prefer.<sup>1243</sup> When different therapists are used to administer different treatments, “such characteristics as age, gender and professional experience should be similar across the sets of therapists administering alternative conditions.”<sup>1244</sup>

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<sup>1241</sup>For a comprehensive analysis of threats to both internal and external validity of research results, see Campbell D, Stanley C. *Experimental and Quasi-Experimental Designs for Research*. Boston; Houghton Mifflin, 1963.

<sup>1242</sup>Berman J, Miler R, Massman P. Cognitive therapy versus systematic desensitization: is one treatment superior? *Psychologic Bull* 97 (1985): 455 ; see also Glass G, Smith M, Miller T. *The Benefits of Psychotherapy*. Baltimore, MD: Johns Hopkins University Press, 1980: (Table 5-25).

<sup>1243</sup>In the study by Berman et al., the lead investigators were not always the therapists. The therapists were often relatively inexperienced trainees.

<sup>1244</sup>Kazdin A. (1986): 99.

Finding therapists experienced in the delivery of currently available treatments is not difficult. Finding therapists with experience delivering psychedelic psychotherapy will be difficult, since training opportunities do not currently exist and currently practicing researchers with experience working with psychedelics legally from the 1950s to early 1970s are few and far between. In discussions with FDA concerning Dr. Grob's proposed study of the use of MDMA in the psychotherapeutic treatment of cancer patients, the need for such training was requested through the use of a small pilot study "to allow [members of] the treatment team to develop their technique in administering the drug and concomitant therapy."<sup>1245</sup> Dr. McCormick was receptive to this proposal and responded "that a case could be made for a pilot study with controls, to establish the effect size in order to appropriately power the main study."<sup>1246</sup>

One note of caution in employing different therapists for different conditions is that Drs. Yensen and Dryer have identified as a potential confound jealous conflicts between treatment staff delivering LSD therapy to inpatient alcoholics and the staff delivering the comparison "routine hospital treatment."<sup>1247</sup> These conflicts, which took place only with inpatients exposed to staff delivering both competing treatments, can be avoided by having the different treatments take place in different locations.

#### Titration of Dose: Different Strategies for the Two Primary Studies

Two major studies of efficacy are usually required to determine the safety and efficacy of a new drug.<sup>1248</sup> These two studies do not need to be identical in design. One important variation between the two major studies testing one form of psychedelic psychotherapy should be the number of doses of psychedelic psychotherapy received by the patients, using a fixed number in one study and a variable number with upper limit in another study. The rationale for the potential value of permitting a variable number of sessions is that therapists could then match the treatment to the depth and speed at which the patient is able to resolve issues of relevance to therapeutic outcome. For example, one study could involve the administration of two experimental sessions to all subjects while the

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<sup>1245</sup>McCormick C. Letter to Dr. Grob. July 23, 1999: 3.

<sup>1246</sup>McCormick C. Letter to Dr. Grob. July 23, 1999: 3.

<sup>1247</sup>Yensen, Donna. (1995): 154.

<sup>1248</sup>After one form of psychedelic psychotherapy has been approved for one patient population, the use of that same form of psychotherapy in a different patient population may require only one large-scale Phase 3 efficacy study. FDA Guidance document, Clinical Evidence for Effectiveness, 10. "(2) Demonstration of Effectiveness by a Single Study of a New Use with Independent Substantiation from Related Study Data, (e) Studies in a closely related disease, (f) Studies in less closely related diseases, but where the general purpose of therapy is similar." However, the Guidance also states, "reliance on only a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible." 13.

second study could involve the administration of 1-4 studies, to be determined by mutual agreement between patient and therapeutic staff.

In FDA's review of the data submitted by Pfizer for the evaluation of Zoloft in the treatment of PTSD, Pfizer's Dr. Farfel indicated that "subjects were dosed once daily beginning with 25 mg/dy in the first week [dosing was not initially based on mg/kg] and then continuing flexibly titrated between 50 and 200 mg/dy thereafter."<sup>1249</sup> Dr. Temple commented about the titration design, indicating that he would have preferred fixed doses. He said, "I would be curious as to why that design was chosen. If it was chosen to avoid adverse effect, that would make some sense, but ordinarily I think you would learn more from a randomization to fixed doses, even if you inched your way up to those doses... Now you could analyze this to see if there was a dose/response hidden in there."<sup>1250</sup> Dr. Hammer, a Pharmacologic Drugs Advisory Committee member, made the suggestion that one of the major studies should have been fixed dose and the other flexible, so as to have gained some information about dose/response relationships in one of the studies.

The fact that the Zoloft design allowed titration suggests that it should also be possible to titrate the number of doses of psychedelic psychotherapy a patient receives in one of the Phase III trials, while holding the number of doses fixed in the other trial.

### Estimating Sample Sizes

One consequence of comparing psychedelic psychotherapy to an approved treatment is that sample sizes needed for determining equivalence are larger than for comparison to placebo. The addition of a fourth arm would therefore increase the expense of the study not only by the addition of all the costs associated with the fourth group but also by increasing sample sizes in all of the groups, especially if the study was powered for superiority rather than equivalence. Nevertheless, the extra cost of adding the fourth arm of the study provides the possibility of neutralizing some of the political opposition to the possible approval of the medical use of a Schedule I drug. Of course, psychedelic psychotherapy would need to demonstrate therapeutic benefits that were equivalent or superior to the more effective medication already available, at least in some subpopulation of patients.

When the difference in efficacy between treatments is small, as in the case where one drug is only marginally more or less effective than the drug or psychotherapeutic treatment to which it is being compared, large sample sizes are needed to detect these small differences. As Dr. A. Lawrence Gould, Merck, Sharp, and Dohme Research Laboratories noted, "Establishing the effectiveness of a therapy for treating an illness ordinarily requires demonstrating that the therapy provides a superior clinical result to some alternative course of treatment such as nothing (or placebo to control for the act of treating) or an alternative

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<sup>1249</sup>Transcript of the October 8, 1999 meeting of the FDA's Pharmacologic Drugs Advisory Committee: 33. <http://www.fda.gov/ohrms/dockets/ac/cder99t.htm#Psychopharmacologic%20Drugs>.

<sup>1250</sup>*Ibid.*, 127.

agent known to be effective. The latter option could require impracticably large sample sizes if the standard and test therapies have similar effects.”<sup>1251</sup>

A review of studies designed to determine if one form of psychotherapy was superior to another indicated that, “Both individual outcome studies and large-scale evaluations of the literature have generated relatively consistent conclusions that alternative treatments produce few differences in treatment outcome.”<sup>1252</sup> This is in part due to inadequate sample size to detect small differences, since, “occasionally, 25 or more subjects per group are included, typically the number averages 20 or fewer.”<sup>1253</sup> The power of a test depends on effect size (the size of the treatment effect as determined by outcome measures, which also depends on the size of the placebo response), sample size, and alpha (level of significance, usually .05).<sup>1254</sup> Dr. Kazdin’s analysis of the effect size in 85 studies comparing the outcomes of different psychotherapies indicated that the average study involved 53.6 subjects in 3.14 groups, or 17.1 subjects per group.<sup>1255</sup> Fully 75% of the studies included fewer than 20 subjects per group. Dr. Kazdin reported that, “If the investigator wishes to compare treatment versus no treatment... A sample size of 27 per group would be needed for the desired power with the median ES [effect size].”<sup>1256</sup> However, “for comparing two treatments [for superiority, not equivalence]...a sample size of 71 per group would be needed to retain power at the desired level for the median ES.”<sup>1257</sup> In the NIMH Treatment of Depression Collaborative Research Program, 250 subjects were allocated to 4 groups, with an average of 62.5 subjects per group. This study was powered to evaluate whether any of the four treatments were superior to each other. Though “there was a consistent ordering of treatments at termination,”<sup>1258</sup> no superior treatment was identified, suggesting the study may have been somewhat underpowered.

Pfizer’s Dr. Gail Farfel reported that for Zoloft, recently approved by FDA for PTSD in a protocol design that compared Zoloft to inactive placebo, “the mean number of subjects in each treatment group was approximately 95,”<sup>1259</sup> although as documents

<sup>1251</sup>Gould A. Another View of Active-Controlled Trials. *Control Clin Trial* 12 (1991): 474.

<sup>1252</sup>Kazdin A. Comparative Outcome Studies of Psychotherapy: Methodological Issues and Strategies. *J Consult Clin Psychol* 54 (1986) 1:102.

<sup>1253</sup>*Ibid.*, 101.

<sup>1254</sup>*Ibid.*, 102. Dr. Kazdin notes that, “Because effect size depends on within-group variability of the observations, any facet of the experiment that can reduce this variability can augment power. Attention to methodological issues such as therapist training, treatment integrity, and selection of a homogeneous set of subjects are examples pertinent to outcome research that can increase precision of the test.”

<sup>1255</sup>Kazdin 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.

<sup>1256</sup>*Ibid.*, 144.

<sup>1257</sup>*Ibid.*, 144.

<sup>1258</sup>Elkin et al. (1989): 971.

obtained from FDA through a Freedom of Information Act request (FOIA) indicate, only about 70 subjects per group completed the trials.<sup>1260</sup> <sup>1261</sup> In a review of the two clinical trials for Zoloft that demonstrated efficacy, Dr. Charles Marmar, Professor and Vice Chairman, Department of Psychiatry, UC San Francisco, noted that “you can see that for the most part the effects, while meaningful, have been modest,”<sup>1262</sup> indicating that sample sizes may need to be fairly large, especially in a comparison study between MDMA and Zoloft.

Dr. Russell Katz, Director of Division of Neuropharmacological Drug Products, stated, “There are conditions where we have considered studies positive or approved drugs on the basis of fairly small studies, but in which the treatment has been statistically significantly different from the control. Of course, the smaller the study, the more likelihood that there is some bias creeping in or that there is an imbalance is an important characteristic that you don’t really know how to test for, you don’t even know what they are necessarily. So we like to see larger studies but there is no specific requirement for numbers.”<sup>1263</sup>

If a comparative treatment is included as a fourth arm in the Phase III protocol design, it is possible that high-dose and/or medium-dose psychedelic psychotherapy would be demonstrated more effective than psychotherapy-only but less effective than conventional treatment or equivalent but not superior. Such findings could complicate FDA’s review process. Nevertheless, a comparative treatment arm should still be included because of the uncertain likelihood of FDA regulatory approval of psychedelic psychotherapy based on a clinical trial that did not test at least for equivalency if not superiority to a conventional treatment.

### The Four-Arm Study Proposal

From the perspective of putting psychedelic medications to a thorough and rigorous test that stands a chance of convincing a skeptical public about the value of psychedelic-assisted psychotherapy, a four-arm study is ideal. Such a study would include a high-dose group, a medium-dose group, a sub-threshold psychotherapy control group, and the most effective currently available medication or psychotherapeutic treatment for the indication being treated. Powering the study to demonstrate superiority of the high-dose psychedelic

<sup>1259</sup> Transcript of the October 8, 1999 meeting of the FDA’s Pharmacologic Drugs Advisory Committee: 32.

<sup>1260</sup> Brady et al. (2000).

<sup>1261</sup> Not all of this data have been published in peer-reviewed journals. This author obtained a complete file of the FDA approval package for Zoloft, through a Freedom of Information Act (FOIA) request. The information on completion rates is from an Oct 19, 1999 memorandum from Thomas Laughren, M.D., Team Leader, Psychiatric Drug Products, Division of Neuropharmacological Drug Products. Subject: Recommendation for Approval Action. Approval Package NDA 19839, S026. (about 200 pages)

<sup>1262</sup> Ibid., 29.

<sup>1263</sup> Ibid., 147.

psychotherapy group to the sub-threshold psychotherapy-only group, and equivalence rather than superiority to the most effective currently available medication, would require smaller sample sizes than would powering the study to be able to reveal superiority instead of just equivalence between the high-dose treatment and the conventional treatment. However, due to the political advantages of being able to demonstrate superiority, a careful review of the number of extra subjects required to power for superiority of the high-dose psychedelic psychotherapy group over conventional treatment should be conducted. If the sponsor of the research can afford the associated increase in costs, these expenditures should be incurred.

The four-arm design described above, used in two independent “adequate and well controlled investigations,” should be sufficient to address the scientific and political concerns about the approval of a psychedelic medicine.<sup>1264</sup> This program of research recalls the NIMH four-arm Treatment of Depression Collaborative Research Program, and would be a rigorous research effort that might help motivate the NIMH to resume its involvement with the field of psychedelic research. As Dr. Laska et al. highlight, “The NIMH traditionally has contributed in major ways to the ongoing process of clinical evaluation of new psychotropic drugs, dating back to the formation of the Psychopharmacology Research Branch (PRB) in the 1960s, the Early Clinical Drug Evaluation Unit (ECDEU) program of the PRB, and including the recently organized Clinical Treatment Research Branch of the NIMH. These federal initiatives have done much to shape the research of the past 30 years involving major drugs in psychiatry.”<sup>1265</sup>

#### Standards of Proof and Protocol Design Criteria: An Unreasonable Burden?

Chapters 4 and 5 have been devoted to a review of regulatory, ethical and methodological issues involved in the design and evaluation of scientific research into the medical potentials of psychedelic psychotherapy. As a result of this review, proposals have been elaborated detailing specific criteria for the design of psychedelic psychotherapy research protocols and rigorous standards of proof for the evaluation of data gathered from any studies that are conducted.

The underlying unevaluated assumption of these criteria and standards has been that they are not in and of themselves so expensive to follow that their practical effect would be to preclude the research and development they are attempting to guide. This issue needs to be considered since at present, sponsors of research into the beneficial medical uses of psychedelics and marijuana have been limited to very small non-profit organizations. Federally-funded studies into the potential benefits of psychedelic drugs ceased over twenty-five years ago<sup>1266</sup> and are not likely to resume any time soon,<sup>1267</sup> although some

<sup>1264</sup>It may also be possible for one quite large multi-center study to be analyzed as two separate studies.

<sup>1265</sup>Laska E et al. (1994): 63.

<sup>1266</sup>Report on ADAMHA Involvement in LSD Research, as cited in Szara, Steven. Are Hallucinogens Psychoheuristic? in *Hallucinogens: An Update, NIDA Monograph Series # 146* Washington, DC, NIH

states have recently allocated money for medical marijuana research.<sup>1268</sup> Certainly the pharmaceutical industry can afford the costs of drug development, but it remains unlikely that the pharmaceutical industry will become involved in these areas of research. Pharmaceutical company interest in marijuana is limited to the use of isolated cannabinoids or marijuana extracts administered in non-smoking delivery systems which can be patented and which sidestep political opposition to the use of the marijuana plant itself as a medicine.<sup>1269</sup> In regard to psychedelic psychotherapy, limiting factors are the controversy attached to psychedelic drugs, their lack of patentability, their use in patient populations too large for Orphan Drug designation,<sup>1270</sup> <sup>1271</sup> and the economic fact that psychedelic psychotherapy will compete directly with conventional products for use in patients. As just

Publication # 94-3872, 1994: 39.

<sup>1267</sup>Personal communication, Shore D. Associate Director for Clinical Research, NIH/NIMH. March 3, 2000. Dr. Shore indicated that it seemed unlikely that NIMH would actually fund psychedelic psychotherapy studies at this time or in the foreseeable future.

<sup>1268</sup>California allocated \$3 million over 3 years to medical marijuana research, with the first funds to be distributed in July 2000 (S.B. 847, passed October 1999, Cal Health & Saf Code § 11362.9 (2000) Marijuana Research Act). San Mateo County, CA has allocated \$350,000 for medical marijuana research, but is still negotiating with NIDA and FDA over protocol design and approval issues. On March 30, 1996, Washington State allocated \$60,000 for medical marijuana research which went unspent by the Dept. of Pharmacy and was returned to the general treasury in 1997. (Downey R. The antidrug mafia makes sure Washington state keeps off the grass. *Seattle Weekly*. June 15-21, 2000.

<http://www.seattleweekly.com/features/0024/news-downey.shtml> )

<sup>1269</sup>Dr. David Hadorn, North American Medical Director of GW Pharmaceutical company, licensed in England to grow marijuana for medicinal purposes, reports that the company plans to develop marijuana-based medicines that are not smoked. Altman L. Company Developing Marijuana For Medical Uses. *NY Times*(Monday, April 10, 2000) A8.

<sup>1270</sup>As just one example, Dr. Bonnie Green, Professor of Psychiatry at Georgetown University Medical School, President-Elect of the International Society for Traumatic Stress Studies (ISTSS), commented that any one time, 5% of women and 2-3% of men have PTSD. At the time of a study ISTSS conducted, there were 4 million women with PTSD. Transcript of the October 8, 1999 meeting of the FDA's Pharmacologic Drugs Advisory Committee: 103.

<sup>1271</sup>Orphan Drug designation has been obtained for marijuana for AIDS Wasting, based on the 200,000 patient population per year threshold. For indications over 200,000 it is at least theoretically possible to obtain Orphan Drug designation by making the case to FDA's Orphan Products Development Office that the funds required for drug development expenses cannot be recovered from sales within the first seven years of marketing. However, only 1 or 2 drugs have been designated as Orphans under this criteria since 1984, when the 200,000 patient population threshold was established. personal communication, Dr. Jack McCormick, Deputy Director, FDA Office of Orphan Product Development, April 14, 2000. Orphan Drug Act of 1983. 97 P.L. 414; 96 Stat. 2049. Jan. 4, 1983.

one example, the use of Zoloft for PTSD has value primarily in the relief of symptoms, with symptoms returning in many patients after medication is withdrawn, necessitating prolonged daily administration.<sup>1272</sup> MDMA-assisted psychotherapy is proposed as an alternative approach to be administered several times to deal with underlying causes, with the goal of making continued medication unnecessary.

What follows is an analysis of the estimated costs of drug development that might be incurred for the development of one clinical use of a psychedelic drug or marijuana.

#### A Range of Estimates from High to Low

Dr. Lester Grinspoon, Harvard Medical School, has claimed that it would take over \$200 million to conduct the studies necessary to make smoked marijuana into a prescription medicine.<sup>1273</sup> Dr. Grinspoon considers this sum unattainable, and argues that marijuana must be legalized for non-medical uses before patients will be able to take full advantage of its medical uses. Dr. Grinspoon asserts that this estimate also applies to other Schedule I drugs such as MDMA.

Fortunately, the sums that Dr. Grinspoon claims will be necessary to bring any Schedule I drug through the FDA drug development process are drastically overestimated. Dr. Grinspoon acknowledges that his estimate is derived from calculations made by Dr. Joseph DiMasi, Tufts Center for the Study of Drug Development.<sup>1274 1275</sup> Dr. DiMasi has reviewed financial information from the pharmaceutical industry in order to determine the average cost of bringing a new chemical entity (NCE) to market. In 1991, Dr. DiMasi estimated that the average cost amounted to \$231 million (in 1987 dollars).<sup>1276</sup> Dr. DiMasi's most recent estimate for the average cost of bringing a drug to market, for 1998, is \$313 million.<sup>1277</sup> Estimates from the pharmaceutical industry have run as high as \$500 million,

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<sup>1272</sup>The FDA has required Pfizer to submit data from a Phase IV study to examine the long-term use of Zoloft in PTSD patients, beyond the 12 week period studied in the trials used as the basis for NDA approval. The December 7, 1999 approval letter from Dr. Russell Katz, Director of the Division of Neuropharmacological Drug Products to Margaret Longshor, Director of Regulatory Affairs, Pfizer, states, "Since post-traumatic stress disorder is regarded as a chronic disease and continued treatment of patients is expected beyond several months, we are interested in reviewing the results of a study which addresses the issue of long-term efficacy. In this regard, we note your November 1, 1999 commitment to submit the results of a long-term relapse prevention trial for our review."

<sup>1273</sup>Grinspoon L. Speech at NORML National Conference, Washington, DC, February 5, 2000.

<sup>1274</sup>DiMasi J, Hansen R, Grabowski H, Lasagna L. Cost of innovation in the pharmaceutical industry. *J Health Econ* 10 (Jul 1991) 2:107-42.

<sup>1275</sup>DiMasi J, Hansen R, Grabowski H, Lasagna L. Research and development costs for new drugs by therapeutic category. A study of the US pharmaceutical industry. *Pharmacoecon* 7 (Feb 1995) 2:152-69.

<sup>1276</sup>DiMasi et al. (1991):132.

<sup>1277</sup>Dr. DiMasi, talk at Harvard Institute for International Development, March 15, 2000.

though Dr. Nelson Levy, ex-head of research and development at Abott Laboratories remarked, “That it costs \$500 million to develop a drug is a lot of bull.”<sup>1278</sup> These sums are well in excess of Dr. Grinspoon’s estimate, but they don’t tell the entire story.

Dr. DiMasi’s estimates are not of out-of-pocket costs but include several components that are not applicable to research and development costs for psychedelics or marijuana. The first such expense included in Dr. DiMasi’s estimates is the opportunity cost of the money the pharmaceutical company has invested over the entire course of the life of the new drug, applying a 9% discount rate. Dr. DiMasi calls this category “income foregone from investing in development for a period before returns are earned (time costs).”<sup>1279</sup> For a sense of the magnitude of these opportunity costs, when they are subtracted from the 1991 estimate of \$231 million, the cost estimate is reduced to \$114 million.<sup>1280</sup> The second such expense is the estimated cost of all the unsuccessful drugs that the pharmaceutical companies tried to develop but abandoned along the way, with the costs of these failures apportioned to the number of drugs that were approved. For an example of the magnitude of these failed efforts, the Office of Technology Assessment has estimated that in general, for every new drug approved by the FDA, pharmaceutical companies synthesize and screen 5000 chemical entities, bring 250 into animal testing, five into human testing, and obtain approval from FDA for only one new medicine.<sup>1281</sup>

Dr. DiMasi calculated in 1995 that from a sample of 93 NCE’s “the capitalized (i.e. out-of-pocket plus time) clinical period costs per approved NCE were \$US70, \$US98, \$US103 and \$US163 million (1993 dollars) for anti-infective, cardiovascular, neuropharmacological and nonsteroidal anti-inflammatory drugs, respectively.”<sup>1282</sup> When the costs of unsuccessful drugs were subtracted out, the mean capitalized costs [leaving opportunity cost of the money still in the calculations] “ranged from \$US7.1 million (for topical steroids) to \$US66.7 million (for cardiovascular agents) [1993 dollars].”<sup>1283</sup> Opportunity costs generally ran about 30-40% of mean capitalized costs, even after unsuccessful drugs have been subtracted out.<sup>1284</sup> While still high, these numbers are no longer so stratospheric.

There is one final factor that reduces the cost estimates even further. Sponsors

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<sup>1278</sup>Gerth J, Stolberg S. Drug Makers Reap Profits on Tax-Backed Research. *New York Times*.(April 23, 2000): A1.

<sup>1279</sup>DiMasi J, Lasagna L. The Economics of Psychotropic Drug Development. in (eds.) Bloom F, Kupfer D. *Psychopharmacology: The Fourth Generation of Progress*.New York: Raven Press, 1995:1890.

<sup>1280</sup>DiMasi et al. (1991): 132.

<sup>1281</sup>Pharmaceutical R & D: Costs, Risks and Rewards, Office of Technology Assessment, Washington, DC, 1993.

<sup>1282</sup>DiMasi et al. (1995):152.

<sup>1283</sup>*Ibid.*,152.

<sup>1284</sup>DiMasi J, Lasagna L. (1995):1891 (Figure 8).

seeking to develop a Schedule I drug like marijuana or MDMA into an FDA-approved prescription medicine have a somewhat ironic opportunity for very substantial cost savings because government health and anti-drug agencies around the world have collectively been investing many millions of dollars annually for decades into research seeking to identify the risks of Schedule I drugs. As Dr. Lasagna has observed, “NIH-supported research represents a subsidy to pharmaceutical development.”<sup>1285</sup> MDMA and marijuana are among the most thoroughly studied compounds in the world. The data about their risks is in the public domain as a result of the studies being primarily funded with public money and published in peer-reviewed scientific journals. There are already over 750 papers in the scientific literature reporting on some aspect of MDMA.<sup>1286</sup> These data can be appropriated by anyone for submission to FDA as part of a package of evidence demonstrating safety and efficacy for a particular clinical indication.

Due to the vast amount of scientific information about the risks of psychedelics and marijuana, the primary research that remains to be gathered for an evaluation of the medical use of these drugs is about the efficacy and safety of the drug in the specific patient population to be treated. The physiological risk profile of the use of the classic psychedelics such as LSD, psilocybin, mescaline, and DMT is already definitively established as being well within acceptable limits. Though controversial, the risk profile of MDMA when used several times as an adjunct to psychotherapy is likely to be acceptable if balanced against demonstrated benefits.<sup>1287</sup> The risk profile of smoked marijuana is the most controversial,

<sup>1285</sup>Gerth, Stolberg (April 23, 2000).

<sup>1286</sup>personal communication, Matthew Baggott, April 8, 2000. Mr. Baggott, UC San Francisco MDMA research team, has been hired by MAPS to catalogue and summarize all published papers on MDMA for submission to FDA and other regulatory agencies.

<sup>1287</sup>The major risk factor associated with MDMA has to do with the reduction of serotonin caused by large doses of MDMA. The most sophisticated investigation of MDMA-neurotoxicity, conducted by Dr. Franz Vollenweider at the University of Zurich, found no evidence for serotonin reductions in several MDMA-naive subjects who were given a PET scan before and after receiving a moderate amount of MDMA (1.5 mg/kg) in the therapeutic dose range. (Dr. Vollenweider’s presentation at Conference on Clinical Research with MDMA and MDE. Dead Sea, Israel. August 31, 1999) Evidence for any functional consequences in animals or humans resulting from even massive consumption of MDMA is weak. Concern centers around several studies that show statistically significant but clinically insignificant reductions in a few memory functions in heavy poly-drug users who have consumed large amounts of MDMA. In the most comprehensive study of MDMA and memory, funded by NIDA, monthly consumption of amounts of MDMA up to 440 mgs/month for several years, a monthly amount well above the therapeutic dose range, was shown to have absolutely no effect on any memory function tested. (Bolla K, McCann U, Ricaurte G. Memory impairment in abstinent MDMA ("Ecstasy") users. *Neurology* 51 (Dec 1998) 6:1532-7.) Recent studies have shown that neurotoxicity is exacerbated by high body temperatures and can be eliminated by a slight cooling of body temperature. Seiden and Malberg had found that serotonin cells

but a reasonable scientific argument can be made that the risk/benefit ratio of smoked marijuana is acceptable,<sup>1288</sup> especially in cases where marijuana is used on a short-term basis

could be protected against neurotoxicity when the researchers lowered the body temperatures of the lab rats. (Malberg J, Sabol K, Seiden L. Co-administration of MDMA with drugs that protect against MDMA neurotoxicity produces different effects on body temperature in the rat. *Pharmacol Exp Ther* 278 (Jul 1996) 1:258-67.) The effect of temperature makes data about neurotoxicity that is gathered from people who take MDMA at raves and exercise vigorously for extended periods of time in high ambient temperature environments of limited predictive value for estimating the risk of subjects exposed to MDMA in clinical settings. (Malberg J, Seiden L. Small changes in ambient temperature cause large changes in 3,4-methylenedioxymethamphetamine (MDMA)-induced serotonin neurotoxicity and core body temperature in the rat. *J Neurosci* 18 (Jul 1, 1998) 13:5086-94.) MDMA's enhanced risk profile is a direct result of its use in recreational settings, with use in clinical research settings relatively non-problematic. (Vollenweider FX, Gamma A, Liechti M, Huber T. Is a single dose of MDMA harmless? *Neuropsychopharm* 21 (Oct 1999) 4:598-600).

<sup>1288</sup>At present, the risk/benefit ratio for smoked marijuana over the oral THC capsule favors marijuana, due to its superior efficacy as a result of its route of administration and the synergistic effect of the range of cannabinoids present in smoked marijuana but not in the oral THC capsule. This risk/benefit calculation will change in the next several years when marijuana extracts delivered in non-smoking delivery systems become available. The major trade-off between the use of smoked marijuana as medicine and the use of marijuana extracts delivered in non-smoking delivery systems will probably be between the increased health risks to the lungs from smoking marijuana and the increased costs involved with the use of extracts delivered in patented non-smoking delivery systems. Efficacy will probably be similar, once marijuana extracts can be delivered sublingually or through the lungs as opposed to the decreased efficacy when swallowed. However, FDA does not take economic factors into account when it reviews drugs for possible prescription use. (personal communication, Dr. Murray Lumpkin, Deputy Center (CDER) Director for Review Management, February 18, 2000) One approach to minimizing the health risks of marijuana to the lungs is the use of more potent marijuana. (Matthias P, Tashkin D, Marques-Magallanes J, Wilkins J, Simmons M. Effects of varying marijuana potency on deposition of tar and delta9-THC in the lung during smoking. *Pharmacol Biochem Behav* 58 (Dec 1997) 4:1145-50.) Another is the use of a simple vaporizer that heats marijuana to a temperature below the burning point of the plant but at which the cannabinoids vaporize out of the marijuana. (Gieringer D. Marijuana Water Pipe and Vaporizer Study. *Bull MAPS* 6 (Summer 1996) 3:59-63. <http://www.maps.org/news-letters/v06n3/06359mj1.html/>) The tobacco industry claims a vaporized delivery system for tobacco can eliminate 80% of some carcinogens. (Nowell R. RJR To Test Reduced-Smoke Cigarette. AP Wire, 4/20/2000.) Marijuana-only smokers, even frequent smokers, have not been shown in epidemiological studies to have a higher risk for lung cancer or an increased mortality rate than non-marijuana smokers. (Sidney S, Beck J, Tekawa I, Quesenberry C, Friedman G. Marijuana use and Mortality. *Am J Pub Health* 87 (1997) 4:585-590). Marijuana smokers, even frequent smokers, do not have an increased risk of chronic obstructive pulmonary disease (COPD). (Tashkin D, Simmons M, Sherrill D, Coulson A. Heavy habitual marijuana smoking does not cause an accelerated decline in FEV1 with age [FEV1 is forced expiratory volume in one second, and is a standard measure of

such as for the control of nausea associated with cancer chemotherapy.<sup>1289</sup>

From 1977-1984, the mean number of subjects enrolled in the clinical trials for drugs approved by FDA was 1450. From 1985-1993, the mean number of subjects had climbed to 3400.<sup>1290</sup> In a study of 12 drugs approved by FDA from 1994-1995, the lowest number of subjects in the clinical trials was 1,000, the highest 13,000.<sup>1291</sup> To put these numbers in context, scientific studies already in the peer-reviewed literature report on clinical investigations of 728 MDMA users, 539 of whom consumed MDMA non-medically and were compared to 484 controls who had not used MDMA, and 189 of whom were administered MDMA in research settings.<sup>1292</sup> Accurately determining the number of marijuana users who have been studied in clinical investigations would be time-consuming but it is probably safe to say the number exceeds 3000.

The discussion of sample sizes earlier in this chapter indicated that for protocols

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age-related change in lung function]. *Am J Respir Crit Care Med* 155 (Jan 1997) 1:141-8.) Marijuana may increase the risk of head and neck cancers, a very rare form of cancer, with the risk greater in marijuana smokers who also smoke tobacco and drink alcohol. (Zhang Z, Morgenstern H, Spitz M, Tashkin D, Yu G, Marshall J, Hsu T, Schantz S. Marijuana use and increased risk of squamous cell carcinoma of the head and neck. *Cancer Epidemiol Biomarkers Prev* 8 (Dec 1999) 12:1071-8.) However, in a recently completed study not yet published but reported in a National NORML press release, Dr. Daniel Ford, Johns Hopkins Medical School, found no association between marijuana and head, neck or lung cancers (NORML Press Release May 25, 2000 <http://www.norml.org/news/archives/00-5-25.shtml>). Dr. Ford was trying to determine if cancer patients were more likely to smoke marijuana or tobacco, or to drink alcohol as opposed to healthy, 'control' patients. Dr. Ford said he thought "[T]he association (between marijuana smoking and cancer) would fall away when we corrected for tobacco use. That was not the case. The association was never there." Dr. Ford also found that "daily marijuana use for a month or more was not associated with increased risk, even among those who never used tobacco." As Dr. Abrams reports, he is "eager to study the extract. But he cautions that, as a pharmaceutical product, its cost may discourage many potential users. "There are always going to be people who are going to perhaps grow their own and use their own medicine," he says. For that reason, "it's still worthwhile looking at the medical effects of smoked marijuana." (Guterman L. The Dope on Medical Marijuana. *Chron High Ed*(June 2, 2000): A21.)

The health risks from smoking marijuana are not zero. Nevertheless, patients who need to administer marijuana on a daily basis may face little or no clinically significant increased health risk if they use higher potency supplies in association with water pipes or vaporizers. It is theoretically possible that patients may save money through the use of less expensive smoked marijuana instead of commercially marketed, patented non-smoking delivery systems for cannabinoid extracts. Money they save may be used on expenditures that improve their health and offset the risks they are assuming.

<sup>1289</sup>Hollister L. Commentary: An Approach to the Medical Marijuana Controversy. *Drug Alcohol Depend* 58 (2000): 3-7.

<sup>1290</sup>Dr. DiMasi, talk at Harvard Institute for International Development, March 15, 2000.

<sup>1291</sup>Peck C. Drug Development-Improving the Process. *Food Drug Law J* 52 (1997) 2:163-167.

<sup>1292</sup>personal communication, Matthew Baggott, April 8, 2000.

designed to assess superiority of one active drug against another, sample sizes in the range of 70 per group may be required. For the purpose of these rough financial calculations, 80 subjects per group will be assumed in a study powered to determine if MDMA-assisted psychotherapy is superior to Zoloft in the treatment of PTSD.<sup>1293</sup> The protocol design for Phase III “adequate and well controlled investigations” for safety and efficacy that is recommended in this chapter is a four-arm study, with an unequal allocation to the psychotherapy-only control group. This would result in three groups with 80 subjects and one group with 40, for a total of 280 subjects, in one of the two required “adequate and well controlled investigations.” Total subjects required in both Phase III efficacy trials for MDMA, and probably for tests of other examples of psychedelic psychotherapy, would thus amount to 560 subjects.

The mean US cost per patient in FDA-approved research was \$5,342 for 1993, \$5,434 for 1994, and \$4,904 for 1995.<sup>1294</sup> In 1996, the mean cost was \$6454, in 1997 it was \$7,123 per subject.<sup>1295</sup> Phase III studies have been reported to cost as high as \$10,000 to \$20,000 per subject.<sup>1296</sup> These costs include the direct expenses of the study but also amortize the large overhead of the major pharmaceutical companies. As a result, these per-subject costs are likely to be substantially higher than the costs that would be incurred by a more budget-minded non-profit drug development entity. Assuming the cost per subject can be brought down to about \$5,000,<sup>1297</sup> the costs of the major studies required by FDA would

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<sup>1293</sup>Until the effect size and variance of response to MDMA-assisted psychotherapy is determined, sample sizes cannot be estimated with accuracy. The more pronounced the treatment effect and the smaller the variation in outcomes, the smaller the sample size needs to be to generate significant results. In order to reduce variance so as to reduce sample size, a homogenous patient population with a relatively uniform response should be selected. In the Zoloft studies, there was a substantial difference in response between men and women. According to Dr. Katz, Director of the Division of Neuropharmacological Drug Products, “The effect of the treatment appears to come from essentially completely from women.” (Memorandum, December 6, 1999 from Director of Division of Neuropharmacological Drug Products to File, NDA 19-839/S-026. Obtained from FDA through FOIA request, along with entire approval package for Zoloft. FOIA Request filed January 20, 2000. Package arrived 4/15/2000.)

The Phase III MDMA studies should be able to avoid this problem through the review of data gathered in the Phase II trials that will evaluate the effectiveness of MDMA in men and in women. The Phase III trials can then be designed either with all men, all women, or a combination. With an advantage in uniformity over the Zoloft designs, it will perhaps be possible to obtain adequate power with 80 subjects in each of the three treatment groups and 40 in the psychotherapy-alone sub-threshold dose condition.

<sup>1294</sup>*Parexel's Pharmaceutical R&D Statistical Sourcebook 1998*. Waltham, MA: Parexel, 1998: 47.

<sup>1295</sup>Dr. DiMasi, talk at Harvard Institute for International Development, March 15, 2000.

<sup>1296</sup>Gerth, Stolberg (April 23, 2000).

<sup>1297</sup>The Phase II MDMA/PTSD dose/response study in Spain will cost \$2,000 per subject. The Spain study involves just one treatment session per subject. It is being administered by a Ph.D. candidate who is

amount to \$2.8 million. This estimate suggests that a total cost of \$5 million might be sufficient, accounting for low estimates and costs for additional animal and human toxicity studies that may be required.

Marinol, the oral THC capsule, was approved by FDA for use as an antiemetic for nausea associated with cancer chemotherapy based on data from 454 patients.<sup>1298</sup> Marinol was approved for the treatment of HIV-associated wasting under the Orphan Drug program based on data from just 130 patients.<sup>1299</sup> The company reports that the cost of developing Marinol for AIDS wasting was \$5 million, but it is difficult to see where all the money was spent.<sup>1300</sup> In England, the pharmaceutical company that is seeking to develop marijuana extracts with non-smokable delivery systems has estimated that the cost to bring the first extract to market in the US is \$16 million.<sup>1301</sup> A large proportion of that sum needs to be devoted to the development of the non-smoking delivery system, an expenditure not required of sponsors seeking to study the use of the marijuana plant itself. The Institute of Medicine report on the medical uses of marijuana commented, "the often-cited cost of new drug development, about \$200-\$300 million, might not apply, but there are probably additional costs needed to satisfy the FDA's requirements for a botanical product."<sup>1302</sup> For example, the chemistry, manufacturing and controls portion of an NDA can be particularly difficult for botanical products but is also rigorous for synthetic drugs. Substantial support for the medical use of smoked marijuana has already come from a handful of funders who have donated approximately \$7 million in support of several state medical marijuana initiatives, in money that is not even tax-deductible since it was donated for election campaigns.<sup>1303</sup> If there were a clear decision by senior federal officials to let the data from medical marijuana research be evaluated on its merits, it should be possible for sponsors interested in studying medical marijuana to raise sufficient funds to conduct the necessary clinical trials.

As this analysis indicates, the amount of money that may be necessary to conduct research into the medical uses of Schedule I drugs, such as marijuana and MDMA, is substantial but is within the range that the non-profit sector could raise. The proposals made in this chapter for specific

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working for little more than living expenses since the study is his dissertation. Under these circumstances, a cost of \$2,000 per subject can be obtained. This is the lower limit for the cost per patient of any MDMA protocol.

<sup>1298</sup>Arky R. (Medical Consultant). *Physicians Desk Reference, 52nd Edition*. Montvale, NJ: Medical Economics Company. 1998: 2545.

<sup>1299</sup>*Ibid.*

<sup>1300</sup>Joy et al. (1999): 203.

<sup>1301</sup>Altman (April 10, 2000).

<sup>1302</sup>Joy et al. (1999):217.

<sup>1303</sup>personal communication, Dr. Ethan Nadelmann., April 25, 2000. personal communication, Dave Fratello, April 27, 2000.

criteria for the design of psychedelic psychotherapy research protocols do not impose an unreasonable burden on sponsors interested in evaluating these medical uses.

#### From Research Design to Regulatory Design

Over the next decade and beyond, numerous psychedelic psychotherapy studies will be conducted. These studies may eventually generate data supporting claims of safety and efficacy. If such claims can be supported by data, how should psychedelic psychotherapy be regulated so that it will indeed on balance make a beneficial contribution to public health?

Chapter 6 will conclude the dissertation with a discussion, well in advance of any practical necessity, of a system of regulatory controls designed to minimize the abuse, misuse, diversion and impact on non-medical use of psychedelics drugs, if any eventually do become approved as prescription medicines.