

A Clinical Plan for MDMA (Ecstasy) in the Treatment of Posttraumatic Stress Disorder (PTSD): Partnering with the FDA

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Abstract—The FDA and the Spanish Ministry of Health have concluded that the risk/benefit ratio is favorable under certain circumstances for clinical studies investigating MDMA-assisted psychotherapy. Both agencies have approved pilot studies in chronic posttraumatic stress disorder (PTSD) patients who have failed to obtain relief from at least one course of conventional treatment. These studies, the only ones in the world into the therapeutic use of MDMA, are being funded by a nonprofit research and educational organization, the Multidisciplinary Association for Psychedelic Studies (MAPS, www.maps.org). A rationale is offered explaining why MAPS chose to focus its limited resources on MDMA, and also on PTSD patients. A Clinical Plan is elaborated for the conduct of the "adequate and well-controlled" trials necessary to evaluate the safety and efficacy of MDMA-assisted psychotherapy for PTSD, with the studies estimated to cost about \$5 million and to take about five years. The Clinical Plan has been developed, in part, through analysis of the studies conducted by Pfizer in its successful effort to have Zoloft approved by the FDA for use with PTSD patients, and through review of transcripts of the FDA's Psychopharmacologic Drugs Advisory Committee meeting that recommended approval of Zoloft for PTSD.

Keywords—Food and Drug Administration, Ecstasy, MDMA, Posttraumatic Stress Disorder

The Multidisciplinary Association for Psychedelic Studies (MAPS, www.maps.org), a membership-based nonprofit research and educational organization, is sponsoring a series of studies designed to develop MDMA into a prescription medicine approved for use by the Food and Drug Administration (FDA), initially for the treatment of posttraumatic stress disorder (PTSD). MAPS is currently sponsoring a pilot MDMA dose-escalation study in Madrid, Spain, with PTSD patients, conducted under the direction of Dr. Pedro Sopolana and Jose Carlos Bouso, Ph.D. candidate (Sopolana & Bouso 1999). This is the world's only ongoing study of the efficacy of MDMA-assisted

psychotherapy. On November 2, 2001, a MAPS-sponsored study under the direction of Dr. Michael Mithoefer was approved by the FDA, with Institutional Review Board (IRB) approval in process (Mithoefer & Wagner 2001). MAPS is also working to sponsor an MDMA/PTSD study in Israel, under the direction of Dr. Moshe Kotler.

This article elaborates a five-year, \$5 million clinical plan outlining a proposed sequence of studies to investigate MDMA-assisted psychotherapy in the treatment of PTSD. This clinical plan starts with pilot studies and concludes with two FDA-required "adequate and well controlled investigations" of safety and efficacy. The present discussion outlines a strategy for developing MDMA into an FDA-approved prescription medicine. A series of regulatory, ethical and methodological issues for the investigation of psychedelic psychotherapy in the context

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of FDA-approved clinical trials, which form the basis for the clinical plan, are discussed in detail in the context of the author's public policy doctoral dissertation (Doblin 2001).

Given the political and scientific hurdles, a rational analysis of the likely return on investment would probably not inspire any venture capitalists to invest their risk capital into the development of MDMA as a prescription medicine. MDMA is off patent, and PTSD or any other psychological disorder for which MDMA might be effective affect more than 200,000 people so that patent protection under FDA's Orphan Drug program cannot be obtained; also, the political hurdles due to MDMA's current nonmedical use may not be surmountable within any time frame that an investor would consider realistic. Though the for-profit approach for the development of MDMA as a prescription medicine is of questionable viability, the non-profit approach is more likely to succeed. There are probably enough philanthropists who, from personal experiences or otherwise, appreciate the political, scientific and medical importance of supporting the struggle to develop MDMA into a legal prescription medicine.

DEVELOPING THE CLINICAL PLAN

This discussion begins by evaluating the strategic advantages associated with conducting FDA-approved research with MDMA for PTSD, as compared to other psychedelics that could be used for psychotherapy and with other potential patient populations. Proposed protocol designs and sample sizes for the studies evaluating the potential use of MDMA in the treatment of PTSD are based in part on a review of documents pertaining to Pfizer's successful development of Zoloft® into the first FDA-approved medicine for the treatment of PTSD. These documents were obtained from the FDA by the author through a Freedom of Information Act (FOIA) request. A FOIA request for FDA documents related to its approval of Paxil for use with PTSD is still pending.

Choosing Drug and Patient Population

The primary strategic issue in conducting psychedelic psychotherapy research is estimating the probabilities of success in the FDA drug development and approval process of any of the numerous combinations of psychedelic drugs and patient populations. Psychedelic drugs, though each with a unique set of actions and side effects, all serve the generally similar function of increasing access to psychological and emotional processes. As a result, psychedelics can be used as general purpose adjuncts to psychotherapy, in the treatment of many conditions for which people seek out psychotherapy or psychiatric treatment. The limited resources available to fund psychedelic psychotherapy research make it essential to choose the best

test case of a specific psychedelic drug used in treating specific clinical indication.

Why MDMA?

On the one hand, the psychological safety profile of MDMA is superior to that of all the other psychedelics. MDMA is relatively short acting, with primary effects lasting only about four hours and gradual return to baseline over the course of another two hours or so. MDMA rarely interferes with cognitive functioning or perception and usually produces a warm, emotionally grounded feeling with a sense of self-acceptance, and a reduction of fear and defensiveness. Subjects under the influence of MDMA can usually "negotiate" with their emergent psychological material and often retain the ability to move at will toward or away from certain thoughts or emotions. In contrast, LSD lasts eight to 10 hours, interrupts rational cognitive processes, impacts perception, requires surrender to inner emotional processes rather than permitting negotiation, and can result in feelings of loss of control, fear and panic (as well as more positive emotions). All the major psychedelics, such as psilocybin, mescaline, ibogaine, DMT, etc., resemble LSD more so than they resemble MDMA. Even the effects of marijuana are more similar to those of the classic psychedelics than to MDMA.

In terms of therapeutic potential, MDMA is remarkably effective, gentle yet profound. Because it operates on emotions more so than cognitive processing, the MDMA state is only subtly different than normal. As a result, the thoughts and emotions of the MDMA state can be easily remembered after the effects of the drug have worn off, facilitating integration and long-term growth. Due to its relative short-acting duration and its gentle action, MDMA has the greatest opportunity of any psychedelic to be integrated into psychiatric practice. The classic psychedelic can be equally or even more therapeutic, but in different ways and with greater personal struggles required of patients and therapists.

On the other hand, the physiological safety profile of all the classic psychedelics is superior to that of MDMA. The extreme position on risk is expressed by Dr. Alan Leshner, former director of the National Institute on Drug Abuse (NIDA), who claims that "There is no safe way to use any of these drugs [such as MDMA]," (Mertl 2000) that "even experimenting with club drugs [such as MDMA] is an unpredictable and dangerous thing to do," and that chronic use of MDMA may cause long-term problems with emotion, memory, sleep and pain (Leshner 2001).

Some recreational users of MDMA (mostly in combination with other drugs) have died from hyperthermia as a result of overheating from vigorous dancing in the high ambient temperature environments of dance clubs with inadequate water or other fluid replacement. From 1994 through 1999, there were a total of 68 MDMA-related

deaths reported to the Drug Abuse Warning Network (DAWN); not all deaths were related to hyperthermia, and MDMA is not established as the causal factor. Medical examiner data has reported one death associated with MDMA in 1994, six in 1995, eight in 1996, three in 1997, nine in 1998, and 41 in 1999 (Office of Applied Studies 2001a). Relatively few of the cases reported by the medical examiner involved MDMA alone; most were associated with MDMA used in combination with one or more other drugs. The medical examiner numbers do not reflect national totals, which do not exist, but are simply the totals reported by the medical examiner offices that are included in the DAWN system. Hospital emergency room visits reported to DAWN as MDMA-related, though not necessarily causally, (these are national estimates) totaled 247 in 1994, 422 in 1995, 319 in 1996, 637 in 1997, 1142 in 1998, 2,850 in 1999, and 4,511 in 2000. (Office of Applied Studies 2001b).

Furthermore, with the exception of ibogaine, the classic psychedelics have not been claimed to be "neurotoxic," as has MDMA. In primates, at doses slightly higher than the amounts used in psychotherapy, MDMA has been linked to minor persisting reductions in serotonin levels in a few brain regions (Ricaurte et al. 1988), with the no-effect level for serotonin reductions in primates being 2.5 mg/kg, administered orally once every two weeks for four months (8X) (Ricaurte, unpublished, cited in Vollenweider et al. 1999a). Whether therapeutic doses of MDMA have any permanent impact on serotonin levels is a matter of substantial controversy (Lieberman & Aghajanian 1999). If high doses of MDMA are consumed frequently (a dosage pattern seen in some recreational users of MDMA), MDMA may reduce serotonin levels for extended periods of time (McCann et al. 1998). Though there is evidence of recovery of serotonin levels over time, serotonin does not reach initial levels in all brain regions, while some brain regions recover to levels higher than baseline (Fischer et al. 1995). Some changes may be permanent (Hatzidimitriou, McCann & Ricaurte 1999). Fortunately for the heavy recreational users of MDMA, these changes in serotonin levels, if they do indeed occur in humans, seem largely asymptomatic. Evidence for any functional consequences in animals or humans resulting from even massive consumption of MDMA is weak. Concern centers around a series of studies that show statistically significant but mostly clinically insignificant reductions in a few memory functions in heavy polydrug users who have consumed large amounts of MDMA (Croft et al. 2001; Gouzoulis-Mayfrank et al. 2000; Gamma 2001; Reneman et al. 2001; Zakzanis & Young 2001; Bolla, McCann & Ricaurte 1998). Concerns that negative functional consequences associated with MDMA use will increase over time as MDMA users age are hypothetical, and are not evidence-based.

Research has shown that neurotoxicity is exacerbated by high body temperatures and can be eliminated by a slight

cooling of body temperature (Malberg & Seiden 1998; Malberg, Sabol & Seiden 1996). The effect of temperature makes data about risk that is gathered from people who take MDMA at raves of limited predictive value for estimating the risk to subjects exposed to MDMA in clinical settings. MDMA's increased risk profile is a direct result of its use in recreational settings, with use in clinical research settings relatively nonproblematic (Vollenweider et al. 1999a). In therapy, MDMA is not used on a daily basis but rather as an adjunct to psychotherapy administered a relatively few times, with several weeks between therapy sessions. The most sophisticated investigation of MDMA neurotoxicity has been conducted by Dr. Franz Vollenweider at the University of Zurich. Dr. Vollenweider found no evidence for serotonin reductions in MDMA-naïve subjects who were given a PET scan shortly before and then again four weeks after receiving a moderate amount of MDMA in the therapeutic dose range (1.5-1.7 mg/kg) (Vollenweider 2001).

The combination of the remarkable therapeutic potential of MDMA, along with its substantial safety for use in clinical settings, makes it a very attractive choice for drug development. A comprehensive risk/benefit analysis that lent support to the case for clinical psychotherapy research with MDMA was funded by MAPS and submitted to the FDA (Baggott, Jerome & Stuart 2001). Politically, however, MDMA is not the easiest psychedelic to try to develop into a prescription medicine. Its nonmedical use is increasing, especially among young people. In the 2001 Monitoring the Future survey, funded by NIDA, 11.7 % of high school seniors reported that they had tried Ecstasy at some point, up from 11.0 % in 2000 and 8.0 % in 1999 (Johnston, O'Malley & Bachman 2001). Police authorities are seizing increasingly large amounts. Customs officials seized 9.3 million ecstasy pills in fiscal year 2000, as compared to 3.5 million in FY 1999 and 750,000 in FY 1998 (Office of Public Affairs, U.S. Customs Service 2000; National Drug Intelligence Center 2000). NIDA has called the increased use of MDMA an epidemic (NIDA 2000).

Yet the political controversy about MDMA offers one crucial advantage that makes MDMA much more likely to become the first psychedelic to be approved as a prescription medicine. As a result of the millions of nonmedical users of MDMA around the world, health authorities, anti-drug authorities and research scientists have expended an amazing amount of time, energy and money trying to understand the risks of MDMA, its mechanisms of action, and the consequences of acute and long-term use.

The number of scientific papers in the peer-reviewed scientific literature reporting on research with MDMA in humans and animals, along with case reports discussing adverse events, exceeds 1,240 according to a Medline search conducted by the author on May 1, 2002. Data in the peer-reviewed scientific literature can be submitted to

FDA as evidence in the assessment of MDMA's risk profile and safety, with the only cost being the time it takes to systematically review the papers and organize the data for submission to the FDA. The FDA is willing to accept published papers for review and has even approved drugs "based primarily or exclusively on published reports" (FDA 1998). The costs of conducting these published MDMA studies is well over \$20 million. The availability of data from these studies dramatically reduces the amount of additional funding that will be required to argue a case before the FDA for MDMA's safety and efficacy.

Several researchers have administered MDMA to human subjects in clinical studies of MDMA's safety, mechanism of action and physiological and psychological effects. More frequently, researchers have compared people who have used MDMA in nonmedical contexts with controls. As of March 2002, more than 262 subjects had been administered MDMA in the context of legal research. There was also data in the scientific literature from more than 985 people who had used MDMA, sometimes in astonishingly large amounts, in nonmedical recreational contexts. These MDMA users have been compared to more than 835 controls.

An MDMA Phase I study with 18 patients has been successfully completed in the United States, although only data on the first six subjects have been published (Grob et al. 1996). Two other Phase I studies with MDMA focused on objectives other than safety have also been conducted in the United States. An MDMA pharmacokinetic study was conducted at the University of California at San Francisco (Everhart et al. 1999), and a study is underway investigating which brain neurotransmitter receptor sites are involved in producing MDMA's subjective effects (Tancer & Johanson 2001). Studies in Switzerland have investigated MDMA's action on brain neurotransmitter receptor sites (Liechti et al. 2000) on information processing (Vollenweider et al. 1999b), and on the psychological and cardiovascular effects of a single dose of MDMA (Vollenweider 1998). Three MDMA pharmacokinetic studies have been conducted in Europe: in England (Fallon et al. 1999), Spain (de la Torre et al. 2000), and Switzerland (Helmlin et al. 1996). A Phase I dose-response safety study has been completed in Spain (Cami et al. 2000; Mas et al. 1999), as well as a study investigating MDMA/alcohol interactions (Hernandez-Lopez et al. 2002). A study investigating the hormonal effects of MDMA has taken place in England (Henry et al. 1998), and a study investigating the immunological effects has taken place in Spain (Pacifi et al. 1999). Yet with all this research, there is not one paper reporting data from a controlled scientific study into the therapeutic use of MDMA.

MAPS' effort to initiate controlled, FDA-approved scientific research into the therapeutic potential of MDMA in patient populations began in 1986, and has taken 16 years to come to fruition. A Phase II dose-escalation pilot study

of MDMA-assisted psychotherapy in the treatment of post-traumatic stress disorder (PTSD) has been approved in Spain. This is currently the only study into the therapeutic use of MDMA approved anywhere in the world. The existence of the Spanish study, sponsored by MAPS, is an important practical factor behind the selection of MDMA as the first psychedelic drug to be the focus of development into an FDA-approved prescription medicine. The sixth patient in the Spanish study, at the 75 mg. dose level, was treated on April 15, 2002. The researchers conducting the study will gather the data in a sufficiently rigorous manner so that it can be submitted to FDA for review. With the approval of this study, the chance to develop the therapeutic potential of MDMA is now more than a mirage.

Why Posttraumatic Stress Disorder?

In choosing the patient population to study, one of the criteria was that the unique properties of MDMA-enhanced psychotherapy needed to be matched to a patient population in which MDMA therapy could offer a dramatic benefit. Ideally, this benefit would require only from one to three drug sessions to produce significant, measurable and long-lasting clinical progress. Alternative medications for this patient population should be relatively ineffective, at least in some subpopulation of patients. The patient population should also be a group that the general public feels compassion towards, in order to help overcome resistance to the idea of the therapeutic use of psychedelics.

The core of the MDMA experience has been described by one of the pioneering psychiatrists who worked with MDMA-assisted psychotherapy in terminal cancer patients as "reducing the fear response to a perceived emotional threat." When used therapeutically, MDMA is administered as an adjunct to psychotherapy on an intermittent basis within a larger therapeutic relationship, usually fewer than four times and frequently only once or twice. Numerous case histories and anecdotal reports testify to MDMA's ability to assist people struggling to come to terms with difficult life events (Stevens 1999/2000; Otalora 1984). These reports suggest that MDMA-assisted psychotherapy should initially be explored not in patients whose psychiatric symptoms originated with biological imbalances with possible genetic components (although MDMA might still be helpful in some ways with such patients), but rather in patients who need some assistance in processing difficult emotions that have a deep component of fear and/or anxiety. Two of the main categories of patients that fit this description are people suffering from PTSD and people facing terminal illness. People with these two types of clinical conditions have been treated with MDMA, sometimes with remarkable results.

The main advantage of working with a PTSD patient population instead of patients with terminal illness is that PTSD patients as a group are probably in better overall health than cancer patients and are taking fewer other

medications, making it less complicated to work with them. Once the MDMA/PTSD study is underway in the United States, MAPS will seek to obtain FDA approval for a study of MDMA-assisted psychotherapy in hospice patients.

In the U.S. market, there are only two conventional pharmacological treatments that have been approved for patients with PTSD. On December 7, 1999, FDA approved the drug known as Zoloft® (sertraline) for PTSD, on the basis of four small clinical trials (it was already on the market as an antidepressant). Two of the clinical trials showed no efficacy, two showed some efficacy. These studies involved a total of 351 subjects. Subgroup analysis revealed that Zoloft was efficacious in female patients but not in male patients. According to Dr. Katz, Director of the Division of Neuropharmacological Drug Products of the FDA, "The effect of the treatment appears to come essentially completely from women (Katz 1999)." On December 14, 2001, FDA approved the use of Paxil® (paroxetine) in the treatment of PTSD. Unlike the Zoloft trials, studies with Paxil showed efficacy in both men and woman. Interestingly, the mechanism of action for both Zoloft and Paxil is to increase the amount in the synapse of the brain neurotransmitter serotonin, the same neurotransmitter that MDMA primarily impacts. The difference is that MDMA increases serotonin acutely for a period of four to eight hours after a single dose, while Zoloft increases serotonin chronically but must be taken on a daily basis.

The patient group that is being tested with MDMA in Spain is composed of women survivors of sexual assault who suffer from chronic PTSD and who have already failed to benefit from at least one course of conventional treatment. The patient group that will be tested in the U.S. will include men and women, survivors of sexual and/or criminal assault, who have failed to benefit from one course of treatment with an SSRI such as Zoloft or Paxil. The patient group for the Israeli study will include patients who have PTSD as a result of war or terrorism, as well as sexual or criminal assault, and who have failed to benefit from one course of an SSRI. By choosing subjects who have already failed on one course of conventional treatment, the risk/benefit ratio is improved in favor of permitting the study to proceed.

The hypothesis is that MDMA will prove helpful in resolving some of these subjects' difficult and painful memories so that they can move forward with some degree of resolution—not forgetting the past, but not burdened by it either. MDMA-assisted psychotherapy also has the potential advantage of being cost-effective, since it can be delivered within a relatively short time.

MDMA in the treatment of PTSD is probably the best combination of psychedelic drug and clinical indication that can most justify a focused drug development effort. What such a drug development plan might look like will be elaborated below, after a brief review of the discussion of

the Psychopharmacologic Drugs Advisory Committee that recommended that Zoloft be approved for use in the treatment of PTSD.

FDA Review of Zoloft for PTSD

Pfizer's recent experience with its successful development of Zoloft for the treatment of PTSD offers the most direct window into FDA policies and procedures for the design of research protocols and the review of data for the pharmacological treatment of PTSD. There are many analogous issues and also important differences between the development of Zoloft, a medication that has been approved by FDA for daily use for the relief of symptoms associated with PTSD, and the development of MDMA, a drug that is meant to be administered from one to three times on an inpatient basis as an adjunct to psychotherapy for the relief of the underlying causes of PTSD. The public record related to FDA approval of Zoloft will be reviewed in order to understand FDA regulatory policy as it applies directly to the development of medications to treat PTSD. The most valuable documents in the public record include transcripts of the October 8, 1999 Psychopharmacologic Drugs Advisory Committee meeting (Psychopharmacologic Drugs Advisory Committee 1999), a slide show delivered at that meeting by Dr. David Smith, Statistical Reviewer, FDA Office of Biostatistics (Smith 1999), and a complete file of the FDA approval package for Zoloft (NDA19839,SO26), obtained from FDA through Freedom of Information Act (FOIA) request. As of May 2002, FDA has not yet responded to a FOIA request for the Paxil approval package.

October 8, 1999 Psychopharmacologic Drugs Advisory Committee Meeting: Study Design Issues

Four clinical trials were reviewed on October 8, 1999 by FDA's Psychopharmacologic Drugs Advisory Committee, which advises the Division of Neuropharmacological Drug Products. Outcome data was presented at the meeting by Pfizer and FDA representatives.

The Advisory Committee meeting began with an overview presented to the Committee by Dr. Tom Laughren, Team Leader for Psychopharmacology at FDA. He indicated that PTSD is a chronic disorder and FDA, "ordinarily uses parallel group studies although one might ask whether a crossover design might be appropriate even for a chronic condition, if the condition is very stable over time and there is a return to baseline if the treatment is stopped" (Psychopharmacologic Drugs Advisory Committee 1999: 10).

Dr. Laughren further noted that, "this is a chronic disorder and one may ask the question whether or not there is a need for long-term data and at what point in development should that information become available should that become an issue for approvability. Now, as an aside, I should say that we never, up until now, made that a requirement

for approving a new indication in psychiatric disorders" (Psychopharmacologic Drugs Advisory Committee 1999: 11).

Dr. Farfel, a Pfizer scientist, indicated that "subjects were dosed once daily beginning with 25 mg/dy in the first week [dosing was not based on mg/kg] and then continuing flexibly titrated between 50 and 200 mg/dy thereafter" (Psychopharmacologic Drugs Advisory Committee 1999: 33). FDA's 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" (Psychopharmacologic Drugs Advisory Committee 1999: 127). Dr. Hammer, 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.

Dr. Laughlen said, "One thing that we like to see for an indication that is more mature in some sense than this is, 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" (Psychopharmacologic Drugs Advisory Committee 1999: 145).

This suggestion of an active control arm for subsequent treatments for PTSD should be adopted. In testing MDMA-assisted psychotherapy for PTSD, parallel groups are more appropriate than a crossover design since the hypothesis is that there will not be a return to baseline after the MDMA treatment is over. This is different for Zoloft, which offers mostly symptomatic relief with a significant number of subjects relapsing once the use of Zoloft is ended. From a financial perspective, this seems ideal for a pharmaceutical company since patients have a continued need to purchase the product or the symptoms will return. In contrast, MDMA-assisted psychotherapy has been helpful in some reported case histories after one to three sessions, with no additional MDMA sessions required to maintain clinical improvement.

The fact that the Zoloft design allowed titration suggests that it might also be possible to titrate the number of doses of MDMA-assisted psychotherapy a patient receives in one of the Phase III trials, to match the treatment to the depth and speed at which the patient is able to resolve issues related to the original trauma.

Sample Size for Efficacy

Dr. Gary Ryan (Group Director of Clinical Research at Pfizer) stated, "Our PTSD Clinical Trial program consisted

of four placebo controlled trials enrolling a total of 757 patients" (Psychopharmacologic Drugs Advisory Committee 1999: 16). Though Dr. Ryan reported a total of 757 patients, the data presented in the slides by Dr. Smith indicated only 597 subjects, with the difference due to attrition. Pfizer's Dr. Farfel reported that, "the mean number of subjects in each treatment group was approximately 95, for a total of 376 subjects treated with sertraline and 381 treated with placebo" (Psychopharmacologic Drugs Advisory Committee 1999: 32).

In the two clinical trials that demonstrated efficacy, a total of 385 patients were enrolled, 191 who received Zoloft and 194 who received placebo (Smith Slide #9). 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 (Psychopharmacologic Drugs Advisory Committee 1999: 29)," indicating that sample sizes may need to be fairly large, especially in a comparison study between MDMA and Zoloft or Paxil.

Dr. Katz, Director of the 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 in 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" (Psychopharmacologic Drugs Advisory Committee 1999: 149).

Sample Size for Safety

Dr. Laughren mentioned that, "this program overall was relatively small, and so in making a judgement about the safety of Zoloft, we relied heavily on the safety experience on other populations. So, a question is, is that a reasonable extrapolation?" (Psychopharmacologic Drugs Advisory Committee 1999: 14) Dr. Farfel commented on safety reporting, "Safety was investigated in 757 subjects, and nothing that was found in this development program suggests a risk that has not already been identified in previous trials and indications, and is already not described in the labeling" (Psychopharmacologic Drugs Advisory Committee 1999: 55).

The minimal number of MDMA-assisted psychotherapy sessions that will be administered to subjects, along with all the safety data already gathered about MDMA from clinical trials around the world, may enable the safety of MDMA in PTSD patients to be investigated with as few subjects as were used in the studies of Zoloft in the treatment of PTSD. This is a reasonable assumption that would change depending on the strength and clarity of the data actually gathered in the clinical studies.

Estimates for Sample Sizes for the Phase III Four-Arm Trials

Based on FDA's review of research into the use of Zoloft in the treatment of PTSD, the power of Pfizer's studies as designed was considered inadequate for subgroup analysis but adequate for group comparisons. The studies as completed had roughly 75 subjects per group. According to Dr. Farfel, the groups had a mean initial enrollment of about 95 subjects, with about 75 per group completing the trial and included in final data analysis.

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 (Friedman, Furberg & Demets 1985). 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. 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 probably be possible to obtain adequate power with 80 subjects in each of the three treatment groups and 40 in the psychotherapy-alone subthreshold dose condition. It might even be possible to use only 70 subjects per group, since Dr. Kazdin has estimated, "for comparing two treatments [for superiority, not equivalence, making this a high estimate for a test of equivalence] . . . a sample size of 71 per group would be needed to retain power at the desired level for the median ES [effect size]" (Kazdin & Bass 1989). Despite the possible use of sample sizes in the range of 70, these estimates have been prepared based on sample sizes of 80.

Duration of Studies

The studies of Zoloft that Pfizer submitted for review were designed as 12-week trials. Dr. Marmar noted that "suicide rates are an important issue both in the acute and chronic form [of PTSD] (Psychopharmacologic Drugs Advisory Committee 1999: 27)," suggesting caution in the use of placebo groups in PTSD patients with a risk factor for suicide. Relatively short treatment courses should be employed to minimize the amount of time patients are receiving placebo, or alternatively psychotherapy alone with a subthreshold dose of MDMA could be used, which would maximize suggestion without providing a direct pharmacological effect of MDMA.

Dr. Domingez (an advisory committee member) suggested that 12 weeks was sufficient for the study since most people respond by then. She noted that there was a

trade-off between the desire to extend treatment in order to give enough time to find an effect and the desire not to keep people on placebo for an unnecessarily long period of time (Psychopharmacologic Drugs Advisory Committee 1999: 129).

This discussion supports limiting the length of MDMA treatment in the clinical trials to 12 weeks, though longer-term follow-up data should also be gathered.

Orphan Drug Designation: Not Possible

Dr. Charles Marmar spoke for Pfizer and stated that the lifetime prevalence for PTSD in the American adult population is 7.8%. 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% to 3% of men have PTSD (Psychopharmacologic Drugs Advisory Committee 1999: 22). Since the adult population of the United States is greater than 170 million, PTSD clearly does not qualify as an Orphan disease since there are more than 200,000 potential patients in any given year.

MAPS' CLINICAL PLAN FOR USE OF MDMA FOR PTSD

The following outline is of a sequence of studies designed to evaluate the risks and benefits of the use of MDMA-assisted psychotherapy in the treatment of post-traumatic stress disorder (PTSD). This plan includes only studies focused on the safety and efficacy of the use of one to four sessions of MDMA-assisted psychotherapy in patients with PTSD. The MAPS Clinical Plan begins with a Phase II study, since Phase I MDMA safety studies have already been conducted in the United States, Spain and Switzerland.

As the studies of MDMA use in patients with PTSD are conducted, additional safety issues may become apparent. Further research addressing specific issues related to the safety of MDMA may be required by the FDA before there will be sufficient information to justify a New Drug Application (NDA). These additional studies, if needed, may involve issues that will be addressed by government-funded research teams around the world already working to assess questions of safety and mechanisms of action. Alternatively, these issues may need to become the subject of research by MAPS-funded scientific teams. However, based on what is already known about MDMA, it is likely that any safety issues related to the use of MDMA in PTSD patients can be adequately addressed by the proposed studies in PTSD patients.

Phase II Dose-Finding Pilot Study in Spain with Women Survivors of Sexual Assault

This study, being conducted by Dr. Pedro Sopelano and Jose Carlos Bouso (Ph.D. candidate, Universidad

Autonoma de Madrid), is currently the only MDMA psychotherapy study underway anywhere in the world in which MDMA is being administered to patients. The goals of this study are (1) to evaluate whether a single dose of MDMA can be administered safely to 29 female survivors of sexual assault with chronic PTSD, (2) to gather preliminary evidence about therapeutic efficacy and, (3) to determine which dose or doses should be used in subsequent larger-scale studies. This study treated the sixth subject on April 15, 2002 and is scheduled to complete the testing of all 29 subjects by May 2003.

The Phase II dose/response study in Spain will cost \$65,000, or \$2,240 per subject. The Spanish study involves just one treatment session per subject. The study is being coordinated by Jose Carlos Bouso, a Ph.D. candidate working on the study for his dissertation. The cost of \$2,240 per subject is the lower limit for the cost-per-patient of any MDMA protocol.

Phase II Full-Dose Pilot Study in the United States with Male and Female PTSD Patients

A research team under the direction of Dr. Michael Mithoefer has worked with MAPS to design and obtain FDA approval for conducting an MDMA/PTSD pilot study in the United States. The protocol was approved by the FDA on November 2, 2001. As of May 2002, the protocol is still in the midst of the IRB approval process. The study should begin in the Summer of 2002. The protocol will involve 20 subjects with PTSD, both male and female. All 20 subjects will receive about 12 hours of non-drug psychotherapy. Twelve subjects will also receive two sessions of MDMA-assisted psychotherapy scheduled three to five weeks apart, with a dose of 125 mgs at each session, while eight subjects will receive two placebo sessions. The goals of this study are (1) to evaluate whether MDMA can be safely administered to PTSD patients and (2) to determine whether there is any preliminary evidence of therapeutic efficacy and, if so, to develop an estimate of the effect size.

The entire treatment course will be conducted in 12 weeks or less, in accordance with the recommendations made in the FDA Psychopharmacologic Drugs Advisory Committee meeting that reviewed the data from the trials of Zolofit in the treatment of PTSD.

If the study does begin in Summer 2002, the research team should be able to complete both sessions for all 20 patients by Summer 2003. The analysis of initial data can be completed by Fall 2003, with six-month follow-up data analysis completed by Winter 2003. The final report can be completed by Spring 2004.

The cost of the study is estimated to be \$12,000 per subject or \$240,000. These costs include non-drug psychotherapy hours and thorough neuropsychological evaluations, as well as substantial costs for administrative work on the FDA and IRB approval process. Subsequent studies will probably require fewer non-drug psychotherapy hours and

may not require any neuropsychological evaluations, depending on the results from this initial pilot study. Since administrative costs have been averaged over a small number of subjects, subsequent studies with much larger subject populations (at least 10 times the size of this pilot study) can be conducted with significantly less cost per patient.

Phase III Trials: Four-Arm Multisite Study in the United States

The goal of this study is to be one of the two primary FDA-required "adequate and well-controlled investigations" demonstrating safety and efficacy of the use of MDMA in patients with PTSD. Depending on the data from the pilot studies, the study will focus either on women, on men, or on both. The study will be designed with a psychotherapy-alone group, receiving a subthreshold (placebo) dose of MDMA, a medium dose group, a full dose group, and a Zolofit or Paxil comparison group.

The number of sessions will be titrated by agreement of patient and therapeutic team, with a maximum of four sessions within a 12-week period. This study will hopefully start in Spring 2004 and will take three years to conduct. The study will enroll approximately 280 subjects, 80 in each drug treatment group and 40 in the psychotherapy-alone group. Due to economies of scale, the study should be able to be conducted for about \$8,000 per subject, for a total cost of \$2,240,000.

Phase III Trials: Four-Arm Study in Spain or Israel

The second large-scale trial will be conducted outside of the United States, in Spain or possibly in Israel. FDA will accept data gathered outside of the United States if it is gathered according to standards set by FDA. With one study conducted in the United States and one in Spain or Israel, it should be possible to obtain marketing approval in both the United States and the European Community.

The goal of this study is to be one of the two primary "adequate and well-controlled investigations" demonstrating safety and efficacy. Depending on the data from the pilot studies, the study will focus either on women, on men, or on both. The study will be designed with a psychotherapy-alone group receiving a subthreshold (placebo) dose of MDMA, a medium dose group, a full dose group and a Zolofit or Paxil comparison group. The study will enroll approximately 280 subjects, 80 in each drug treatment group and 40 in the psychotherapy-alone group (see below for rationale for this estimate). This study will involve a fixed number of sessions administered within a 12-week period. It will involve three sessions for each subject, once every four weeks, with no titration permitted. The use of two different designs for the two different Phase III studies, with the U.S. study using a variable number of treatment sessions depending upon patient and therapist decision and the foreign study employing a fixed number of three sessions, is based on the recommendation made

by Dr. Hammer during the October 8, 1999 meeting of FDA's Psychopharmacologic Drugs Advisory Committee.

This study will hopefully start in Spring 2004 and will take three years to conduct. The study will enroll 280 subjects and should cost in the range of \$8,000 per subject, for a total cost of \$2,240,000.

Total Cost

The total cost of the sequence of studies enumerated above amounts to \$4,720,000. Additional animal or human toxicity studies may be needed, though it is likely that these

studies will have already been government-funded with the data in the public domain.

The clinical plan elaborated above suggests that a rough estimate of about \$5 million will need to be expended over a five-year period to develop MDMA into a prescription medicine for just one clinical indication, PTSD. After MDMA is approved initially for PTSD, one adequate and well-controlled multisite investigation might be sufficient for the approval of subsequent uses of MDMA in closely related disorders, such as in the psychotherapeutic treatment of anxiety and depression in cancer patients.

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