Rick Doblin, Ph.D.
MAPS Executive Director
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[redacted]

To: Dr. Michael James, Chairperson
Bellberry Human Research Ethics Committee

Ref No: 2011-12-607
Re: February 29, 2012 letter to Dr. Stuart Saker

Dear Dr. James,

By way of introduction, I'm Rick Doblin, Ph.D., Executive Director of MAPS, the non-profit research and educational organisation that is the global sponsor working with PRISM to initiate research in Australia into the use of MDMA-assisted psychotherapy in the treatment of posttraumatic stress disorder (PTSD). I've a Ph.D. in Public Policy from the Kennedy School of Government, Harvard University, with a dissertation focused on the regulation of the medical uses of Schedule 1 drugs such as MDMA (which is the equivalent of Schedule 9 in Australia).

I'm writing to respond to the Bellberry HREC review and rejection of the research protocol, "A Randomised, Double-Blind, Active Placebo-Controlled Phase 2 Pilot Study of MDMA-Assisted Manualised Psychotherapy in Australian War Veterans with Chronic, Treatment-Resistant Posttraumatic Stress Disorder (PTSD)". I believe that all the concerns regarding the design of the protocol and our overall approach to the development of MDMA for PTSD that were raised in the February 29, 2012 letter to Dr. Saker can be adequately addressed and that the protocol can ethically proceed as designed. This letter is the start of a process of engaging in a dialogue with you and the other members of the HREC. I can see in retrospect that it would have been best if either I or Steve McDonald had participated in your phone call with Dr. Saker.

MAPS is sponsoring an international series of Phase 2 pilot studies in order to develop MDMA into a prescription medicine to be administered under the direct supervision of trained male/female co-therapist teams. MAPS has sponsored promising Phase 2 MDMA/PTSD pilot studies in Spain, the US, Switzerland and Israel, and is working to start additional Phase 2 pilot studies in Canada, Australia and England. MAPS' Director of Clinical Research, Amy Emerson, has extensive experience working in the pharmaceutical industry, monitoring clinical trials for Novartis and other major pharmaceutical companies.

Your letter indicated a concern that Dr. Saker lacked research and study design experience. We recognise that and don't consider it to be a problem. We select our PIs for their effectiveness in delivering MDMA-assisted psychotherapy according to our treatment manual and adherence criteria and we provide standardised therapist training plus comprehensive support in study design and in the conduct of research. MAPS staff, in association with PRISM staff, have designed the protocol and will monitor the clinical trial according to

GCP/ICH standards. All of MAPS' international protocols are also submitted for review and approval to the US Food and Drug Administration (FDA) and we anticipate that the FDA will audit the data. As a result, you can be assured that Dr. Saker will be provided with the support and expertise necessary to ensure that the study will be conducted to rigorous standards that can withstand critical scrutiny.

I'll address below each of the issues raised as concerns of the Bellberry HREC.

SAMPLE SIZE

Your letter stated, "The basis for this study is the Mithoefer publication in J Psychopharmacology. That was a very small, placebo-controlled trial which showed promising results. It is not clear why further development would not simply expand that study rather than conducting another small study which in this case, is underpowered according to the sample size calculation provided in the protocol. In this regard, the study does not meet the requirements of the NHMRC National Statement on Ethical Conduct in Human Research section 1.1(b). This was a critical issue for the Committee."

In the US, we chose not to expand the initial Mithoefer study which was mostly in women survivors of childhood sexual abuse and adult rape and/or assault. Rather, MAPS has initiated a new, ongoing three-arm dose-response study to be conducted by Dr. Michael Mithoefer in 24 US veterans, firefighters and police officers with chronic, treatment-resistant PTSD. We're seeking to learn whether MDMA-assisted psychotherapy as described in our treatment manual can be effective in war-related PTSD as we have already shown that it can be effective in PTSD from childhood sexual abuse and adult rape and assault. We have also changed the design from an inactive placebo which did not produce a successful double-blind, to a three-arm study with groups receiving either low, medium or full doses of MDMA, which preliminary data suggests is producing a more effective blind. Whether our treatment can be effective regardless of the cause of PTSD, and how to design a successful double-blind, are several of the key issues that we need to address in our Phase 2 studies, to guide the inclusion criteria and design of our eventual Phase 3 studies. We also wish to ensure that our standardised treatment can be delivered effectively to other populations of people with PTSD. Therefore, we saw no value in directly replicating or simply expanding our initial Mithoefer study.

Another key issue for MAPS in our series of Phase 2 studies is determining whether co-therapist teams other than the Mithoefers can replicate the results that they obtained. The Australian study is also designed to evaluate whether we can produce a successful double-blind in a two-arm study. We see no need for the Australian study to be powered to obtain statistically significant results, especially since we will be conducting a pooled analysis, combining the data from our Australian study with data from our other Phase 2 pilot studies. FDA requires data from Phase 3 studies to demonstrate sufficient safety and efficacy to justify approval for prescription use. The purpose of Phase 2 studies is to guide the design of the pivotal Phase 3 studies, not to provide statistically significant data to use to justify prescription approval.

Your letter claimed that it was unethical for us to conduct a Phase 2 study underpowered for statistical significance, and you cited the NHMRC National Statement on Ethical Conduct in Human Research section 1.1(b). However, Section 1.1(b) of the NHMRC statement does not specify merit in terms of protocol power or specifics of study design. That section says that

research that has merit is "(b) designed or developed using methods appropriate for achieving the aims of the proposal." While Phase 3 studies must be powered to gather statistically significant results, Phase 2 studies can and do have other aims.

The aims of the study under review do not include obtaining statistically significant results about efficacy. Rather, in the part of the protocol that discusses our aims, we say we are seeking to gather information about trends toward efficacy, not statistically significant evidence of efficacy. These trends do not need to be statistically significant to provide useful information to guide the design of our Phase 3 studies. Here is the relevant text from our protocol:

"*3.0 Protocol Hypothesis, Aim and Objectives*

The overall hypothesis to be tested in this study is that a full dose of MDMA used in conjunction with psychotherapy will attenuate PTSD symptoms as evaluated by standard clinical measures, when compared with an active placebo dose of MDMA used in conjunction with psychotherapy.

The specific hypotheses to be tested by the proposed study are stated below.

1. Volunteers receiving full-dose MDMA-assisted psychotherapy will experience (trends toward) a greater decrease in signs and symptoms of PTSD than active placebo controls after each experimental session, as measured by the Clinician-Administered PTSD scale (CAPS), the self-reported Impact of Events Scale and Symptoms Checklist-90-R (SCL-90-R)

2. Volunteers receiving MDMA-assisted psychotherapy will experience (trends toward) a greater decrease in signs and symptoms of PTSD than controls at two months after the second drug-assisted (full-dose MDMA or active placebo) session."

There is nothing unethical about conducting Phase 2 pilot studies that are underpowered for efficacy when the aim of the study explicitly focuses on trends, rather than statistically significant results. Furthermore, MAPS uses the same primary outcome measure in all of its PTSD studies, the CAPS, and many of the same secondary measures. Our planned analysis of the pooled data will generate additional information about efficacy using data from the Australian study.

FUNDING

Your letter stated that another concern was that, "The letter from MAPS indicates the study is not fully funded and this added to the committee's concerns on the merits of proceeding."

Like PRISM, MAPS is also a non-profit organisation that raises funds from donations. As I am sure you realise, it's virtually impossible to raise all the funds for a study that is not yet approved. Nevertheless, should this study become fully approved, we will start and complete it, even if we don't manage to raise all the funds from donations restricted to this specific study. MAPS has cash reserves of over $1 million which can be allocated to projects should our fundraising for specific studies fall short. In addition, MAPS has been given a bequest of about $5 million for MDMA research, with the first disbursement of $3.2 million already received. MAPS' Board of Directors has reserved these funds for our Phase 3 MDMA/PTSD studies, which will cost more than $10 million. Having these funds for Phase 3 will make it

easier for MAPS to raise funds to complete our international series of Phase 2 studies, and will also make it easier for MAPS to raise the remaining funds for Phase 3.

Your letter also stated, "During the phone interview, you indicated that it was costly for your time to run the study and therefore, the sample size was kept to the minimum possible. This response, which did not draw on a statistical argument, was a concern to the Committee which felt the response reflected a lack of research and study design experience."

As I've indicated previously, we are aware that Dr. Saker lacks research and study design experience. The protocol has been diligently designed by MAPS and PRISM to detect trends towards efficacy while contributing data to our multi-study meta-analysis.

What follows below is some or all text from your February29, 2012 letter and our response to each point.

1. What is the rationale for the active placebo rather than a genuine placebo as used in the original Mithoefer study? What is the evidence that a dose of 30 mg MDMA with 15 mg supplemental dosing would be a placebo?

The "genuine" placebo that we used in the Mithoefer study was ineffective. Unlike most clinical research studies, we explicitly gather data about the guesses of the subjects and therapists concerning whether the subject was randomly administered the placebo or an active drug. We've also now started gathering guesses from the independent raters. In the original Mithoefer study, the investigators correctly guessed subject condition all of the time and subjects guessed correctly nearly all of the time.

In contrast, data from a completed MAPS-sponsored MDMA/PTSD study in 12 subjects conducted in Switzerland that used an active placebo dose of 25 mg with a supplemental dose of 12.5 mg, as compared to 125 mg with supplemental dose of 62.5 mg, did produce a successful double-blind. In the 25 mg condition, there was a 46% rate of correct guesses, almost perfectly random. In the 125 mg condition, there was a 66% rate of correct guesses, close to random.

The rationale for both doses is presented in Section 2.4 of the study protocol and refers to previous research in healthy volunteers. Literature about the administration of MDMA to healthy humans in Phase 1 studies, described in the protocol and the Investigator's Brochure, also indicate that 30 mg MDMA can serve as an active placebo.

2. The crossover from low dose to the high dose presupposes there will be a benefit from the high dose compared with the low dose. This design lacks objectivity. Before the crossover of the low dose group to the stage 2 higher dose study, there should be analysis of stage 1 results. If the low dose ("active placebo") group has at least as good an outcome as the higher dose group, the crossover would have no merit. Also, if an individual has shown significant improvement on the low dose MDMA, there is no benefit for that individual to switch to the higher dose MDMA.

The presence of Stage 2 is not predicated on there being a benefit from full dose MDMA. Rather, it is firstly intended to increase subject retention through the roughly 4 months of the low dose/ placebo condition by assuring participants that they have the option to receive the study drug and treatment should they choose to do so after the completion of Stage 1, and

secondly it uses subjects as their own controls to gather information comparing low and full dose.

Results from Stage 2 will not be treated as part of the main analysis, and so conclusions about the treatment will be based upon Stage 1 results. Having Stage 2 will not interfere with drawing those conclusions. Anyone who feels they have benefitted sufficiently from the low dose MDMA can discontinue the study if they so wish and then complete the long-term follow up. People who choose to discontinue the study after completing Stage 1 will not be replaced.

To ensure reliability of the CAPS measures at the end of Stage 1, we have intentionally not conditioned eligibility for Stage 2 on any specific cut-off score on the CAPS. We are concerned that doing so might cause subjects who want to participate in Stage 2 to bias how they report their symptoms during the CAPS interview at the two-month follow-up.

Regarding the comment that there would be no benefit to subjects from participating in Stage 2 if they have improved in Stage 1, we have seen in the initial Mithoefer study, and also in the Swiss study, that subjects who demonstrated clinically significant improvement in Stage 1 often went on to demonstrate further clinically significant declines on the CAPS in Stage 2.

To require a full analysis of the Stage 1 results before permitting subjects in Stage 1 to enrol in Stage 2 would involve lengthy delays that could exceed one year or more that would compromise the purpose of Stage 2. We believe it would be unethical to require subjects who have completed the two-month follow-up after Stage 1 to refrain from seeking other treatments for their PTSD for a year or longer should they decide to participate in Stage 2. Otherwise, new treatment approaches would introduce variables that obscure the comparison of Stage 1 results with Stage 2 results. In addition, the lengthy delay would reduce subject retention through Stage 1.

3. *It was not clear that it would be practical to administer the large number of measuring instruments and this was not made any clearer during the phone interview.*

In our direct experience, it has been practical to conduct studies with this number of measures. This study includes a group of four outcome measures that are administered by the independent rater, and three others that are completed by the subject at different times during the study. After screening, it should take no more than an hour and a half to complete the four outcome measures, and some of the measures, such as the SOCQ, are not completed at this time. Only the CAPS and PDS both assess PTSD symptoms, with the CAPS considered the primary outcome measure, while all other measures assess separate factors, such as depression, sleep quality and quality of life, and cannot be reduced down to fewer measures. The study underway in the US also employs four outcome measures, including the CAPS, PDS and PSQI and a measure of posttraumatic growth.

4. *For an appropriate risk:benefit profile, the trial should be reserved for those with genuine treatment-resistant PTSD. However, the inclusion criteria allow entrance of those who have failed only one treatment approach and could have had a diagnosis of PTSD for only 6 months. At interview, you agreed that these criteria could be altered to ensure that only treatment resistant patients were recruited.*

Past and current findings do not support the conclusion that research with MDMA-assisted psychotherapy is particularly risky. We have shown in our initial US study, our Swiss study, and our initial Israeli study that the risks are minimal. No drug-related serious adverse events have arisen in any of these studies, and beyond the occasional use of anxiolytic "rescue medication", no medical interventions have been required for adverse events occurring during the study. Results from the US pilot study show that there is no evidence of declines in neurocognitive performance as gathered in comprehensive pre- and post-trial neurocognitive evaluations. In our view, a rational risk:benefit analysis would conclude that the risks are not so great as to require limiting enrolment to the most treatment-resistant subjects. This argument has been accepted by FDA, our US IRB, the Israeli Ministry of Health and our Israeli Ethics Committee.

Regarding the requirement of a diagnosis of PTSD of at least six months, that standard is the widely accepted time at which PTSD is considered chronic. We think this is a reasonable standard that is used in numerous PTSD research protocols.

We see no reason related to risk:benefit profiles to require subjects to have had a diagnosis of PTSD for more than six months, or to require subjects to have failed on more than one treatment approach. However, if there is an adequate number of PTSD patients in Australia who meet a more expansive definition of treatment-resistant, we can accept such changes to the protocol.

5. *The Committee questioned whether it is ethical to undertake studies of the type proposed if the test agent is unlikely to be approved for registration by regulatory agencies. In the current regulatory environment, it is unlikely that government agencies will approve a racemic mixture for registration without gaining substantial knowledge relating to the individual enantiomers (PK, PD, included AEs). Given the potential hurdles posed by regulatory authorities, should the sponsors and investigators consider comparing the individual enantiomers with the racemic mixture and placebo? At the very least the sponsor should acknowledge that such information will be required and that the current study is only part of the total process. If there is no intention of undertaking supporting studies relating to separate enantiomers, it raises questions about the usefulness of another small study on racemic MDMA.*

This comment is predicated on the assumption that regulatory agencies will not approve a racemic mixture of MDMA "without gaining substantial knowledge relating to the individual enantiomers (PK, PD, included AEs)." However, examining the available legislation does not support this assumption. Even if it were true, there has already been substantial research on the enantiomers of MDMA. In addition, it is not clear why low likelihood of drug approval should preclude performing a study since there is a low likelihood that any drug entering clinical research will ever become an approved prescription medicine.

RACEMIC OR ENANTIOMER RESEARCH

The concern about the necessity of supporting studies comparing the individual enantiomers with the racemic mixture has never been expressed to us by regulatory agencies in the US, Switzerland or Israel. We find no such requirement in FDA regulations, see: http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/FDCActChapterVDrugsandDevices/ucm108125.htm

We would appreciate it if you could provide us with references that support your statement that racemic mixtures will not be approved by the TGA without substantial research in human clinical trials with each of the individual enantiomers investigating PK, PD and AEs. We'd also appreciate information about whether such studies are, in your view, required in healthy volunteers in Phase 1 studies as well as in Phase 2 studies in patient populations.

In any case, the published, peer-reviewed scientific literature already includes a fair number of studies investigating various aspects of the enantiomers of MDMA, including data on the relative bioavailability of individual enantiomers. We are attaching a list of references to this literature for your review.

ETHICS OF RESEARCH AND POTENTIAL FOR APPROVAL

The concept that research is ethical only if it is likely that such research will lead to approval for registration by regulatory agencies contradicts our understanding of the entire drug development process. Most drugs that are researched in the context of Phase 1 studies do not go on to become prescription medicines. Since simple statistics show that it is not likely that a drug that enters Phase 1 will become a prescription medicine, it would seem that all such Phase 1 research is unethical if the basis for ethical research is contingent on the drug being likely to become approved by regulatory authorities.

According to a 2001 report by the Tufts Center for the Study of Drug Development, "Of every 5,000 medicines tested, according to the Pharmaceutical Research and Manufacturers of America, only five on average are tested in clinical trials. Based on research by the Tufts Center for the Study of Drug Development, only one of these five is eventually approved for patient use." These statistics show that there is only a 20% chance that a drug entering Phase 1 becomes an approved prescription medicine. A more recent study, Trends in Risks Associated with New Drug Development: Success Rates for Investigational Drugs published in 2010 by DiMasi, Feldman, Seckler and Wilson indicates a similar rate of success.
It is therefore a low likelihood that any drug that enters Phase 1 will become an approved prescription medicine.

According to an article by Dominic Barnes, Vice President, Medical and Scientific Affairs, Janssen-Cilag Australia, and part-time General Practitioner, Sydneyhttp://www.australianprescriber.com/magazine/29/6/159/61, "Drug discovery, development and commercialisation is a long, expensive and risky process both for the sponsoring company and the trial participants involved. For each successful entrant to the market, thousands of compounds fail to survive the testing and regulatory review process, however, the rewards for successful innovation can be substantial."

At least in the US, Switzerland, Israel and Canada, institutional review boards or ethics boards have never required "likelihood of [treatment/drug] registration" as a point for approving a study. This conclusion is left up to the respective national regulatory agencies in charge of scheduling or registering drugs and medications. The concern is not an element of study design, and it does not affect participant safety.

6A. The question above relates to a broader question of the merits of conducting a new underpowered study and how that could possibly contribute to a development program aimed at getting regulatory approval for use of MDMA in PTSD.

MAPS' drug development program for MDMA-assisted psychotherapy for PTSD involves an international series of Phase 2 studies investigating a number of methodological issues. These issues must be addressed before we are in a position to propose the design of our Phase 3 trials to FDA in the context of an End-of-Phase 2 meeting. Our Australian protocol is designed to gather information on several of these issues and can do so effectively without increasing the power of the study to gather statistically significant data.

The issues we are seeking to learn more about in our Phase 2 studies include:

1. What is the mean magnitude and variance of the treatment effect combining data from multiple different male/female co-therapist teams?
2. What is our treatment method itself - will it include two or three experimental sessions?
3. How do we design a successful double-blind study? Can we have a successful double-blind in two-arm studies or will we require designs with three arms?
4. Are there cultural differences in response to MDMA-assisted psychotherapy?
5. Is our treatment method independent of the cause of the PTSD?
6. Are our adherence criteria and therapist feedback systems sufficient to ensure that therapists across different study sites are delivering the non-drug therapy in a sufficiently similar manner?

We can gather valuable data relating to all of these issues from our Australian study as currently designed, without having to increase size and cost for statistical significance. [Note also that the study is part of a series of studies and is not intended to stand alone or provide all the information we are interested in.]

6B. "The Committee also discussed the facilities in the context of this trial. While there is no specific problem, it was seen as preferable that such a study that requires overnight stays and frequent observation is best conducted in a fit-for-purpose facility. Most large academic institutions (universities, public hospitals) have dedicated drug study units and facilities. Also, interaction and input from more investigators such as might occur in an academic environment was seen as preferable to a sole investigator conducting the study in his private rooms. The NHMRC National Statement sections 1.1(e) and (f) outlines that research that has merit is conducted or supervised by persons or teams with experience, qualifications and competence that are appropriate for the research, and conducted using facilities and resources appropriate for the research."

We certainly agree that the research should be conducted in a setting that is conducive to the requirements of the study. We take great care in creating settings that support the therapeutic process and provide all the safety equipment such as crash carts and related equipment. While academic and hospital settings do offer certain advantages, we have found that specially outfitted private offices often provide a more conducive setting with increased privacy, comfort, and quiet. Our US, Swiss and Canadian studies were (or shall be) conducted in private offices furnished for overnight stays. Our Israeli study is being conducted at the largest mental hospital in Israel but we've found that problematic since there is a stigma for people to go for treatment to a locked facility known as a mental hospital for profoundly mentally ill patients. Fortunately, we've recently been given exclusive access to a small building on the edge of the hospital grounds, which we are customising for our study.

We also agree that research is ideally conducted by teams. MAPS has assembled an outstanding clinical research team including experts in psychiatry, regulatory affairs, clinical research design and monitoring, statistics, and we have the world's expert on the peer-reviewed scientific literature on MDMA on MAPS' full-time staff. We've attached a document listing the members of our clinical research team. We have a track record of successful clinical trials with the results of the Mithoefer study already published, a paper about the results of our long-term follow-up to the Mithoefer study accepted with requests for minor revisions, and the results of our Swiss study currently under review, all at a peer-reviewed journal indexed in Medline.

In summary, we believe that the proposed study has scientific merit and that the risks of study participation are low and balanced out by potential benefits. We look forward to further discussions with you regarding our replies to your concerns. We hope that we can come to agreement on a way to enable this important study to go forward. Please note that I'm happy for all future correspondence to occur through PRISM.

Sincerely,

Rick Doblin, Ph.D.
MAPS Executive Director

Attachments:

1. MDMA Enantiomer Studies
2. MAPS Research Staff

MDMA ENANTIOMER STUDIES

Human studies of enantiomer effects of MDMA and MDE [related compound]

Absolute configuration and psychotomimetic activity.
Anderson GM 3rd, Braun G, Braun U, Nichols DE, Shulgin AT.
NIDA Res Monogr. 1978;(22):8-15.

Enantio-selective cognitive and brain activation effects of N-ethyl-3,4-methylenedioxyamphetamine in humans.
Spitzer M, Franke B, Walter H, Buechler J, Wunderlich AP, Schwab M, Kovar KA, Hermle L, Grön G.
Neuropharmacology. 2001 Aug;41(2):263-7

Human studies of the stereoselective metabolism of MDMA **racemate**

Stereospecific analysis and enantiomeric disposition of 3,4-methylenedioxymethamphetamine (Ecstasy) in humans.
Fallon JK, Kicman AT, Henry JA, Milligan PJ, Cowan DA, Hutt AJ.
Clin Chem. 1999 Jul;45(7):1058-69. Erratum in: Clin Chem 1999 Sep;45(9):15

Simultaneous determination of amphetamine, methamphetamine, methylenedioxyamphetamine (MDA), methylenedioxymethamphetamine (MDMA), and methylenedioxyethylamphetamine (MDEA) enantiomers by GC-MS.
Hensley D, Cody JT.
J Anal Toxicol. 1999 Oct;23(6):518-23

Drug Testing in Blood: Validated Negative-Ion Chemical Ionization Gas Chromatographic-Mass Spectrometric Assay for Enantioselective Measurement of the Designer Drugs 3,4-Methylenedioxyamphetamine, 3,4-Methylenedioxymethamphetamine (MDMA), and 3,4-Methylenedioxyethylamphetamine and Its Application to Samples from a Controlled Study with MDMA
Peters FT, Samyn N, Lamers CT, Riedel WJ, Kraemer T, de Boeck G, Maurer H
Clinical Chemistry 2005,51(10):1811-1822

Stereochemical Analysis of 3,4-Methylenedioxymethamphetamine and Its Main Metabolites in Human Samples Including the Catechol-Type Metabolite (3,4-Dihydroxymethamphetamine).
Pizarro N, Farré M, Pujadas M, Peiró AM, Roset PN, Joglar J, De La Torre R
Drug Metabolism and Disposition 2004,32(9):1001-1007

Determination of MDMA and its Metabolites in Blood and Urine by Gas Chromatography-Mass Spectrometry and Analysis of Enantiomers by Capillary Electrophoresis
Pizarro N, Ortuno J, Farre M, Hernandez-Lopez C, Pujadas M, Llebaria A, Joglar J. Roset PN. Mas M. Segura J. Cami J, de la Torre R
Journal of Analytical Toxicology 2002,26(3):157-165

Stereochemical analysis of 3,4-methylenedioxymethamphetamine and its main metabolites in human samples including the catechol-type metabolite (3,4-dihydroxymethamphetamine).

Pizarro N, Farré M, Pujadas M, Peiró AM, Roset PN, Joglar J, de la Torre R.
Drug Metab Dispos. 2004 Sep;32(9):1001-7.

Determination of MDMA and its metabolites in blood and urine by gas chromatography-mass spectrometry and analysis of enantiomers by capillary electrophoresis.
Pizarro N, Ortuño J, Farré M, Hernández-López C, Pujadas M, Llebaria A, Joglar J, Roset PN, Mas M, Segura J, Camí J, de la Torre R.
J Anal Toxicol. 2002 Apr;26(3):157-65

Stereoselective urinary MDMA (ecstasy) and metabolites excretion kinetics following controlled MDMA administration to humans.
Schwaninger AE, Meyer MR, Barnes AJ, Kolbrich-Spargo EA, Gorelick DA, Goodwin RS, Huestis MA, Maurer HH.
Biochem Pharmacol. 2012 Jan 1;83(1):131-8. Epub 2011 Sep

Studies of MDMA Enantiomers in Nonhuman primates

Behavioral and neurochemical consequences of long-term intravenous self-administration of MDMA and its enantiomers by rhesus monkeys.
Fantegrossi WE, Woolverton WL, Kilbourn M, Sherman P, Yuan J, Hatzidimitriou G, Ricaurte GA, Woods JH, Winger G.
Neuropsychopharmacology. 2004 Jul;29(7):1270-81

3,4-Methylenedioxymethamphetamine (MDMA, "ecstasy") and its stereoisomers as reinforcers in rhesus monkeys: serotonergic involvement.
Fantegrossi WE, Ullrich T, Rice KC, Woods JH, Winger G.
Psychopharmacology (Berl). 2002 Jun;161(4):356-64. Epub 2002 Apr 19

In vivo pharmacology of MDMA and its enantiomers in rhesus monkeys.
Fantegrossi WE.
Exp Clin Psychopharmacol. 2008 Feb;16(1):1-12.

Tyr-95 and Ile-172 in transmembrane segments 1 and 3 of human serotonin transporters interact to establish high affinity recognition of antidepressants.
Henry LK, Field JR, Adkins EM, Parnas ML, Vaughan RA, Zou MF, Newman AH, Blakely RD.
J Biol Chem. 2006 Jan 27;281(4):2012-23. Epub 2005 Nov 3

Characterization of 3,4-methylenedioxymethamphetamine (MDMA) enantiomers in vitro and in the MPTP-lesioned primate: R-MDMA reduces severity of dyskinesia, whereas S-MDMA extends duration of ON-time.
Huot P, Johnston TH, Lewis KD, Koprich JB, Reyes MG, Fox SH, Piggott MJ, Brotchie JM.
J Neurosci. 2011 May 11;31(19):7190-8

Reinstatement of extinguished amphetamine self-administration by 3,4-methylenedioxymethamphetamine (MDMA) and its enantiomers in rhesus monkeys.
McClung J, Fantegrossi W, Howell LL.
Psychopharmacology (Berl). 2010 May;210(1):75-83. Epub 2010 Mar 23.

Endocrine and neurochemical effects of 3,4-methylenedioxymethamphetamine and its stereoisomers in rhesus monkeys.
Murnane KS, Fantegrossi WE, Godfrey JR, Banks ML, Howell LL.
J Pharmacol Exp Ther. 2010 Aug;334(2):642-50. Epub 2010 May 13.

The neuropharmacology of prolactin secretion elicited by 3,4-methylenedioxymethamphetamine ("ecstasy"): A concurrent microdialysis and plasma analysis study.
Murnane KS, Kimmel HL, Rice KC, Howell LL.
Horm Behav. 2012 Feb;61(2):181-90. Epub 2011 Dec 1

Chronic treatment with a serotonin(2) receptor (5-HT(2)R) agonist modulates the behavioral and cellular response to (+)-3,4-methylenedioxymethamphetamine [(+)-MDMA].
Ross JD, Herin DV, Frankel PS, Thomas ML, Cunningham KA.
Drug Alcohol Depend. 2006 Feb 1;81(2):117-27. Epub 2005 Jul 28.

In vivo detection of short- and long-term MDMA neurotoxicity - a positron emission tomography study in the living baboon brain.
Scheffel U, Szabo Z, Mathews WB, Finley PA, Dannals RF, Ravert HT, Szabo K, Yuan J, Ricaurte GA.
Synapse. 1998 Jun;29(2):183-92.

The role of human UDP-glucuronyltransferases on the formation of the methylenedioxymethamphetamine (ecstasy) phase II metabolites R- and S-3-methoxymethamphetamine 4-O-glucuronides.
Schwaninger AE, Meyer MR, Zapp J, Maurer HH
Drug Metab Dispos. 2009 Nov;37(11):2212-20. Epub 2009 Aug 10.

Hyperthermia induced by 3,4-methylenedioxymethamphetamine in unrestrained rhesus monkeys.
Taffe MA, Lay CC, Von Huben SN, Davis SA, Crean RD, Katner SN.
Drug Alcohol Depend. 2006 May 20;82(3):276-81. Epub 2005 Nov 11.

Estimating the relative reinforcing strength of (+/-)-3,4-methylenedioxymethamphetamine (MDMA) and its isomers in rhesus monkeys: comparison to (+)-methamphetamine.
Wang Z, Woolverton WL.
Psychopharmacology (Berl). 2007 Jan;189(4)483-488.

S*tudies involving administration of MDMA enantiomers or stereoselective metabolism of the racemate in rats and mice*

Differential effects of intravenous R,S-(+/-)-3,4-methylenedioxymethamphetamine (MDMA, Ecstasy) and its S(+)- and R(-)-enantiomers on dopamine transmission and extracellular signal regulated kinase phosphorylation (pERK) in the rat nucleus accumbens shell and core.
Acquas E, Pisanu A, Spiga S, Plumitallo A, Zernig G, Di Chiara G.
J Neurochem. 2007 Jul;102(1):121-32.

Differences in the stimulus properties of 3,4-methylenedioxyamphetamine and 3,4-methylenedioxymethamphetamine in animals trained to discriminate hallucinogens from saline.
Callahan PM, Appel JB.
J Pharmacol Exp Ther. 1988 Sep;246(3):866-70.

Disposition of methylenedioxymethamphetamine and three metabolites in the brains of different rat strains and their possible roles in acute serotonin depletion.
Chu T, Kumagai Y, DiStefano EW, Cho AK.
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MAPS RESEARCH STAFF

Multidisciplinary Association for Psychedelic Studies:

Clinical Staff

Rick Doblin PhD

Founder and Executive Director, MAPS

Rick Doblin, Ph.D., is the founder and Executive Director of the Multidisciplinary Association for Psychedelic Studies (MAPS). He received his doctorate in Public Policy from Harvard's Kennedy School of Government, where he wrote his dissertation on the regulation of the medical uses of psychedelics and marijuana and his Master's thesis on a survey of oncologists about smoked marijuana vs. the oral THC pill in nausea control for cancer patients. His undergraduate thesis at New College of Florida was a 25-year follow-up to the classic Good Friday Experiment, which evaluated the potential of psychedelic drugs to catalyze religious experiences. He also conducted a 34-year follow-up study to Timothy Leary's Concord Prison Experiment. Rick studied with Dr. Stanislav Grof and was among the first to be certified as a Holotropic Breathwork practitioner. His professional goal is to help develop legal contexts for the beneficial uses of psychedelics and marijuana, primarily as prescription medicines but also for personal growth for otherwise healthy people, and eventually to become a legally licensed psychedelic therapist. He founded MAPS in 1986, and currently resides in Boston with his wife and three children. Doblin works with the clinical team in research development and support.

Amy Emerson BS

Director of Clinical Research

Amy earned her BS in genetics and cell biology from Washington State University. She has worked in clinical development and research for the last 15 years in the fields of immunology (Applied Immune Sciences), oncology (RPR), and most recently in vaccine development (Chiron and Novartis). Amy has worked with MAPS as a volunteer since 2003 facilitating the development of the MDMA clinical program. She is currently working as Director of Clinical Research and is involved with creating the structure needed to support the growing needs of the clinical operations group and MAPS clinical research studies. Emerson monitors and supports studies in the US and Israel. Amy works with the clinical team to manage research development.

Julie Holland MD

Medical Monitor

Dr. Julie Holland is a board certified psychiatrist in New York City. As an undergraduate at the University of Pennsylvania, Dr. Holland majored in the "Biological Basis of Behavior," a series of courses combining the study of psychology and neural sciences, with a concentration in psychopharmacology, or drugs and the brain. In 1992, Dr. Holland received her medical degree from Temple University School of Medicine, where she performed research on auditory hallucinations, extensively interviewing nearly 100 psychotic patients. In 1996, she completed a psychiatric residency at Mount Sinai Medical Center, where she was the creator of a research project treating schizophrenics with a new medication, obtaining an IND from the Food and Drug Administration. In 1994, she received the Outstanding Resident Award from the National Institute of Mental Health. She

has been an Assistant Clinical Professor of Psychiatry at the NYU School of Medicine from 1996 to the present. She is a Medical Monitor for MAPS-sponsored studies of MDMA-assisted psychotherapy and marijuana (cannabis) as a pharmacotherapy for PTSD.

L. (Ilsa) Jerome PhD

Clinical Research and Information Specialist

Ilsa earned a Ph.D. in psychology from the University of Maryland. She helps MAPS and researchers design studies, gathers information on study drugs through keeping abreast of the current literature and discussion with other researchers, creates and maintains documents related to some MAPS–supported studies, and helps support the MAPS psychedelic literature bibliography. She has written informational documents on psilocybin, LSD and MDMA. She compiles and submits study documents to regulatory agencies. She is interested in using methods from behavioral science and neuroscience to learn how humans feel and think about themselves and each other. Ilsa works with the clinical team to support protocol development and data analysis.

Ann T. Mithoefer BSN

Co-investigator for MDMA/PTSD studies

Annie Mithoefer, B.S.N., is a Registered Nurse living in Charleston, SC, where she divides her time between clinical research and outpatient clinical practice specializing in treating posttraumatic stress disorder (PTSD) with an emphasis on experiential methods of psychotherapy. She is a Grof-certified Holotropic Breathwork Practitioner and is trained in Hakomi Therapy. Recently she and her husband, Michael Mithoefer, M.D., completed a MAPS-sponsored Phase II clinical trial testing MDMA-assisted psychotherapy for PTSD. A paper about their study was published in the Journal of Psychopharmacology. They are currently conducting a clinical trial with veterans who have PTSD resulting from service in the U.S. Armed Forces, as well as a psychotherapy training program for MAPS researchers.

Michael C. Mithoefer MD

Clinical Investigator for MDMA/PTSD Studies, Medical Monitor

Michael Mithoefer, M.D., is a psychiatrist practicing in Charleston, SC, where he divides his time between clinical research and outpatient clinical practice specializing in treating posttraumatic stress disorder (PTSD) with an emphasis on experiential methods of psychotherapy. He is a Grof-certified Holotropic Breathwork Facilitator and is trained in EMDR and Internal Family Systems Therapy. He and his wife, Annie Mithoefer, recently completed a MAPS-sponsored Phase II clinical trial testing MDMA-assisted psychotherapy for PTSD. A paper about their study was published in July 2010 in the Journal of Psychopharmacology. They are currently conducting a clinical trial with veterans who have PTSD resulting from service in the U.S. Armed Forces, as well as a psychotherapy training program for MAPS researchers. Dr. Mithoefer is the Medical Monitor for MAPS-sponsored clinical trials in Europe, the Middle East, Canada, and Colorado. Before going into psychiatry in 1995 he practiced emergency medicine for ten years, served as medical director of the Charleston County and Georgetown County Emergency Departments, and currently holds a clinical faculty position at the Medical University of South Carolina. He is currently board certified in Psychiatry, Emergency Medicine, and Internal Medicine.

K. Linnae Ponte BA

Executive and Clinical Assistant

Linnae earned her BA in Biological Psychology from New College of Florida in May 2010 where she defended her thesis, which investigated the impact of sleep disturbance in the pathogenesis of depression in a sample of 360 students. During her undergraduate years, Linnae assisted data collection and analysis of various projects at University of South Florida's Cardiovascular Psychophysiology Laboratory, MOTE Marine Mammal Aquarium Psychophysical Laboratory, East-West College of Natural Medicine, and the West Mamprusi Civic Union in Ghana, West Africa. Linnae served as New College's Counseling & Wellness Center Student Representative and is continuing her studies through CIIS' Integral Counseling Psychology Weekend Program. Linnae supports work on special projects within the clinical team.

Berra Yazar-Klosinski PhD

Lead Clinical Research Associate

Berra earned her Ph.D. in Molecular, Cell and Developmental Biology from the University of California, Santa Cruz in 2010, and utilizes her scientific training and experience in for-profit pharmaceutical research to help lead MAPS' clinical team to develop, design, and implement clinical psychedelic research in the U.S and beyond. She earned her B.S. in Biological Science from Stanford University, with an emphasis on the neurobiology of drugs. Prior to entering graduate school, Berra worked as a Research Associate with Geron Corporation screening for drugs that activate telomerase, and with Millennium Pharmaceuticals on Phase 1 clinical trials to treat Acute Myeloid Leukemia. Berra joined MAPS in order to work with an organization where profit wouldn't dictate the agenda of scientific research. Berra leads the clinical team under direction of the Director of Clinical Research to develop and conduct MAPS clinical trials.

Contractors

Yvonne Michel, PhD

Statistician and statistics consultant

Yvonne Michel obtained a PhD in biostatistics from the Medical University of South Carolina. Michel was employed as an Associate Professor at the College of Nursing, MUSC. She has taught Masters and PhD students research methods and experimental design for over 16 years. Dr. Michel participated in numerous research projects resulting in over 60 publications in referred nursing and medical research journals and acted as reviewer/editorial board member for three nursing journals. Dr. Michel retired from academia in 2007 and now acts as a consultant for nursing research and quality improvement projects in hospitals and other nursing/medical areas. Michel has acted as consultant for MAPS during all stages of research development, from study design to data analysis.

Mark T. Wagner PhD

Neuropsychologist and assessment expert

Mark Wagner is a licensed clinical psychologist. He earned his doctorate in clinical psychology, specializing in neuropsychology, from Memphis University in 1985. He has practiced at Medical

University of South Carolina since 1992 and currently holds the position of Professor of Neuroscience in the Division of Neurology. He had been the director of the Psychological Assessment Center at MUSC from 1992 to 2001 in the Department of Psychiatry and Behavioral Sciences. Since 2001 he has been the Director of Neuropsychology in the Division of Neurology and is engaged in clinical care, teaching and research. Wagner is a member of the International Neuropsychological Society, the American Psychological Association, Division of Clinical Neuropsychology and the National Academy of Neuropsychology. Wagner has acted as investigator, co-investigator or consultant for clinical and other research trials and has published extensively. Wagner has been a co-investigator in the MDMA-assisted psychotherapy trials with Michael Mithoefer MD and has been one of the independent raters. He is an integral part of training other independent raters to perform the primary outcome measure of PTSD symptoms, the Clinician-Administered PTSD Scale (CAPS).