MDMA-assisted psychotherapy, prior Phase I research and in accounts of psychotherapy performed prior to the scheduling of MDMA in the US [1-3]. The supplemental dose is also identical to the one used in the US study. The initial dose is expected to produce all the common effects of MDMA, including changes in affect (mood) and cognition and changes in feelings of interpersonal closeness and trust. The supplemental dose will prolong subjective effects without producing physiological effects any greater than peak effects occurring after the initial dose.

Active placebo MDMA doses have been selected on the basis of their ability to produce minimal but detectable subjective effects [4, 5] and thus serve as an active placebo. The cumulative dose of 37.5 mg MDMA is expected to produce slight alterations in consciousness, as slight increases in tension or relaxation, but without producing a significant reduction in anxiety or a significant increase in access to emotionally upsetting material [5].

As described above, capsules containing the initial dose of MDMA will be administered in the offices of Dr. Pacey at approximately 10:00 AM. Supplemental doses will be administered upon mutual agreement by the investigators and participant one and a half to two and a half hours after the initial dose. There will be no take-home doses. The investigators may decide not to administer the supplemental dose of MDMA if they believe that the participant exhibits signs or symptoms suggesting that an additional dose of MDMA could produce a serious adverse event.

There will not be any changes in dose regimen across the three MDMA-assisted sessions. If the participant experienced hypertension that required clinical intervention or had a serious adverse event during an experimental session, then no further doses of MDMA will be administered.

S Drug Substance

S.1 General Information

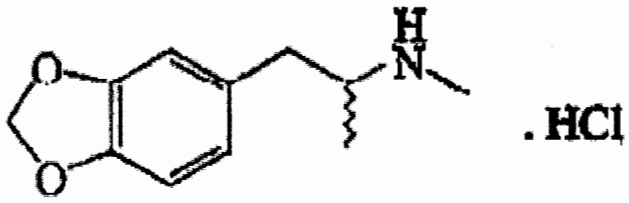
The drug product is (+/-)-(3,4)-methylenedioxymethamphetamine HCl, also referred to as N,-alpha-Dimethyl-1,3- benzodioxole-5-ethanamine, and is described by the chemical formula $C_{11}H_{15}NO_2$. The drug is a white, crystalline powder. The drug will be administered orally in capsules. The product to be used in this study was synthesized by [Lipomed AG, Switzerland, in 12.98 (batch Nr. 94.1B5.51) with a purity of 99.66% (see Analysis Data Sheet Lipomed 11.05.99). MDMA from this lot has been used previously in human studies conducted by Switzerland. On January 30, 2006, a quality control analysis was performed by This analysis reconfirmed identity, purity and content of MDMA HCl Lipomed Batch no with no decomposition products detectable and a HPLC purity >98%.

S.1.1 Nomenclature: MDMA is a ring-substituted isopropylamine. It is also referred to as a phenethylamine. Other names for MDMA are methylenedioxy-n-

methylamphetamine, N-methyl-3,4-methylenedioxyphenylisopropylamine, and N-Methyl-methylenedioxyamphetamine.

It is an entactogen, and its chief pharmacological actions are serotonin, norepinephrine and dopamine release and inhibition of uptake.

S.1.2: Structure: The drug product is described by the chemical formula $C_{11}H_{15}NO_2$. The image below is the diagram present on a data sheet from the manufacturer, Lipomed AG.



The drug product is chiral and possesses two enantiomers, R-(-)-MDMA and S-(+)-MDMA. The drug product will be administered as a racemate. To date, all clinical trials have administered the racemate, and street "ecstasy" (illicitly manufactured MDMA) also consists of the racemate.

S 1.3 General Properties: The molecular weight of MDMA is 193.25.

The specified melting point is 149 +/- 3 C (from manufacturer), and melting point of the batch was

It is water soluble.

MDMA is a white crystalline powder. It is administered as a salt, as MDMA HCl.

S.2 **Manufacturer**: As stated above, the manufacturer is the Swiss company Lipomed AG. The address for Lipomed AG is Fabrikmattenweg 4, CH-4144, Arlesheim, Switzerland. Their website is http://www.lipomed.com

S.2.1 Method of Manufacture (see also p. 1 of report).

Step 1: 3,4-methylenedioxybenzaldahyde + nitroethane -> MDA-nitrostyrol
Step 2: MDA-nitrostyrol + LiAlH4 -> MDA
Step 3: MDA + methylchloroformiate -> MDA-methylcarbamate
Step 4: MDA-methylcarbamate + LiAlH4 -> MDMA

Information on manufacturing process, description of manufacture, assessing purity and stability are contained within the report provided by

S.2.3 Control of Materials

See above and contained in report by

S.3 Characterization:

Batch number is

S.3.1 Elucidation of Structure and Other Characteristics

Quality analysis was performed twice by . One report was written on Feb 23, 2006 and the second on July 23, 2008.

In a quality analysis, both high-performance liquid chromatography (HPLC) and gas chromatography-mass spectroscopy (GC-MS) were used to assess the purity of the drug product.

Structure: performed HPLC and GC-MS to determine if the substance conformed to manufacturer standards. He found that both tests matched confirmation of 99% with no impurities detected (p. 2).

Validation: From manufacturer, data available upon request

Specifications: The batch met all manufacturer specifications, including visual appearance, melting point and purity, as specified in manufacturer document.

Purity: HPLC, >99% with no decomposition products detected

S.3.2 Impurities

On the manufacturer's data sheet, residual solvents listed were isopropyl alcohol at < 100 ppm and isopropyl ether at < 2000 ppm. No impurities were detected in the analyses conducted by and listed above.

S.4 Control of the Drug Substance

S.4.1 Specifications

These are listed on the manufacturer's data sheet.

Appearance: White crystalline powder
Identity: IR

UV, in distilled water: $\lambda_{(Max)}$=1 234 +/- 1 nm
ϵ_{mol} = 3800 +/- 500
Melting Point: 149 +/- 3 C
Purity HPLC = 98.5%
Free base content = > 82.5%
Water content: 0.3 +/- 0.3%
Calculated hydrochloride content: 15.81%
Residual solvents: Isopropyl alcohol< 5000 ppm, isopropyl ether < 5000 ppm

S.4.2 Analytical procedures: These analytical procedures were used by

HPLC
HP 1090 DAD; Column = Spherisorb ODS-1, 3 µm,125 x 4 mm i.d.; mobile phase; H_2O: Acetonitrile; HP_3O_4 85%; hexylamine = 928.72: 5: 0.28 mL: isocratic flow 0.8 mL/min at 40 C.
Injection volume: 10 µL
Detection: 198 nm
Identification: DAD spectrum 192-350 nm vs. standard

GC/MS
Column: DB-5ms, 25 m X 0.2 mm i.d., film = 0.33 µm
Temperature program: 60 C (2 min hold) - 250 C at 20 C/min, 250 C (5 min hold)
Carrier gas: He1.2 mL/min
Derivatization: MBTFA
Injection: 250 C, splitless 1 µL
Detection: full scan

Identity (HPLC-DAD): TR = 7 min, GC/MS TR = 10.6 min (MDMA-TFA) m/z 135, 154 (basepeak), 162, 289 (M^+, MDMA-TFA)
Purity (HPLC): >99% with no decomposition products detected

S.4.3 Validation of Analytical Procedures

Validation upon request from

S.4.4 Batch Analysis:

Provided on manufacturer's data sheet

Appearance: Conforms to appearance
Identity: IR identical to reference
UV, in distilled water, $\lambda_{(MAX)}$.1 = 234.0 nm
ϵ_{mol},1 = 3939
$\lambda_{(Max)}$.2 = 285.0 nm
ϵ_{mol}.2 = 3688
Melting point = 148.9 to 149.7 C

Purity HPLC = 99.66%
Freebase content: 83.51%
Water content: 055%
Calculated hydrochloride content: 15.81%
Residual solvents: Isopropyl alcohol < 100 ppm
Isopropyl ether < 2000 ppm

S.4.5 Justification of Specification

Specifications are those listed by the manufacturer. The manufacturer produces MDMA used in human research studies in Europe and the US, including other sponsor-supported studies. The manufacturer has experience producing pharmaceutical-grade MDMA.

S.6 Container Closure System

The study drug, with or without inactive ingredient, will be placed in opaque capsules and these will be stored in bottles stored by the principal investigator.

S.7 Stability

S.7.1 Stability Summary and Conclusions

There is stability data for this batch of MDMA, performed by and a report on another source of MDMA also provides relevant information on the long-term stability of MDMA, as the material in that report was tested 19 years after synthesis, storage, and opening and removal of MDMA from its container. These reports indicate that MDMA is extremely stable for up to 20 years and possibly longer. assessed sample purity and found it remained greater than 99% pure with no decomposition detected. In his report, reported that a sample of MDMA HCl assessed with HPLC also remained 99% pure over a 19-year period.

S.7.2 Stability protocol and stability commitment

Given the summary described above and the data below, it appears that MDMA possesses considerable long-term stability of at least 2 years and potentially 20 or more years.

S.7.3 Stability Data

reports (p. 2) that there is no sign of degeneration 24 months after production when assessed on July 30, 2008.

also assessed purity on August 2006, and compared it with manufacturer's assessment made in December, 1998, and reported >99% with no decomposition products detected.

P. Drug Product

The drug product will consist of capsules containing racemic 3,4-methylenedioxymethamphetamine (MDMA) in the following dosages: Experimental dose initial dose 125 mg MDMA per capsule; experimental dose supplemental dose 62.5 mg MDMA per capsule; active placebo initial dose 25 mg MDMA plus lactose to reach equivalent weight of 125 mg capsule per capsule; active placebo supplemental dose 12.5 mg MDMA plus lactose to reach weight of 62.5 mg per capsule. There are no other ingredients in these capsules. The capsules will be prepared using the MDMA manufactured by Lipomed AG, Arlesheim, Switzerland, but will be compounded by a Vancouver-area pharmacist.

The sponsor has based dosage on previous research studies (2, 4) and on narrative reports of MDMA-assisted therapist (as Adamson and Metzner 1980; Stolaroff 2004). A dose of 125 mg has been used in a previous sponsor-supported research study conducted in the US (3). The sponsor chose the active placebo dose on the basis of a previous research study (4), with 25 mg expected to produce very few effects. The sponsor selected an inactive material to help maintain the blind by ensuring that all doses are of equal weight.

P.3 Manufacture

The manufacturer, manufacturing procedure and batch number are the same for the drug substance as those listed above in the quality summary.

P.3.1 Manufacture(s)

Capsules will be compounded at a pharmacy in British Columbia. The study drug will be compounded and will not be re-synthesized. The encapsulation will be performed by an individual possessing the appropriate skills, as a pharmacist. The MDMA will be weighed out (calculated as the weight of the hydrochloride salt) into gelatin capsules in combination with lactose, used to ensure that all capsules have similar weights. All capsules will contain the exact weight of MDMA and a varying amount of lactose to maintain equal weights between active placebo and experimental dose capsules.

P.3.3 Batch Formula

Opaque capsules will be filled with the appropriate dose of MDMA.
Experimental initial dose: 125 mg
Experimental supplemental dose: 62.5 mg
Active Placebo initial dose: 25 mg + approximately 100 mg lactose or appropriate amount so that full weight = 125 mg
Active placebo supplemental dose: 12.5 mg + 50 mg lactose or appropriate amount so that full weight = 62.5 mg
Capsules placed in numbered bottles

P.4 Control of Excipients

Lactose will be included as an inactive ingredient in all "active placebo" doses of the product. Active placebo doses of MDMA will contain lactose to ensure that active placebo and experimental dose MDMA capsules are of equal weight.

P.4.1. Specifications

All doses of MDMA will be in the form of opaque capsules. There will be no other material other than MDMA or lactose in any capsules for this study. There will not be any preservatives, coloring agents or any other active ingredients.

P.7 Container Closure System

All doses of MDMA will be in the form of opaque capsules. The capsules will be within plastic bottles with caps. Each bottle will be assigned a number intended for use in the randomization process so as to maintain the double blind. Each bottle will contain All bottles will be appropriately stored in the offices of the principal investigator.

MDMA will be handled in accordance with all provincial and national regulations and forms pertaining to the use of controlled substances in Canada, and will be maintained by the investigators. The MDMA will be stored in a locked safe and only the therapist-investigators will have access to the drug product. All doses will be prepared in a manner to ensure that the investigators cannot distinguish between Low and Fully Active dose capsules.

A Attachments:

1. Lipomed sheet listing specifications and batch analysis
2. Quality Analysis of ; pp. 1-2 concern this batch of MDMA and p. 3 concerns capsules produced for a sponsor-supported study in Switzerland
3. Stability report of referring to different source and batch of MDMA but supporting long-term stability

1. Cami, J., et al., *Human pharmacology of 3,4-methylenedioxymethamphetamine ("ecstasy"): psychomotor performance and subjective effects [In Process Citation].* J Clin Psychopharmacol, 2000. **20**: 455-66.
2. Greer, G. and R. Tolbert, *Subjective reports of the effects of MDMA in a clinical setting.* J Psychoactive Drugs, 1986. **18**: 319-27.
3. Mithoefer, M., *MDMA-assisted psychotherapy in the treatment of posttraumatic stress disorder (PTSD): Eleventh update on study progress.* MAPS Bulletin, 2008. **17**: 11-12.
4. Grob, C., *Unpublished data on human study of psychological and physiological effects of MDMA.* 2001.
5. Harris, D.S., et al., *Subjective and hormonal effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans.* Psychopharmacology (Berl), 2002. **162**: 396-405.

Health Canada / Santé Canada

Office of Clinical Trials

Screening Template for CTA - 30-day default review

CR File #: **9427-M2544-21C**	DSTS Control #: **126833**
Date received in OCT : 2008.12.22 Review 1 Start Date: **2008.12.24**	Due Date: **2009.01.23**
Study Phase: Phase II-30 day	Data Description: CL/2VO/2CD
Study Population: Males, Females	Clinical Division: Vol. # 1
Document I.D. #: 543517	Quality Division: Vol. # 2
PSEAT Format: PDF	
PSEAT Template Path: I:\SOAMES_MUOP\MDMA_MAPS\NewWork\126833_cta.doc	

RECEIVED
DEC 24 2008

Product Name : **MDMA**

Protocol # or Identifier: MM-P4 CH

Protocol Title: A Randomized, Active Placebo-controlled Pilot Study of 3,4 methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD)-Canada

Therapeutic/Pharmacological Classification: Monoamine releaser and uptake Inhibitor
[Clinical Group II : CNS]

Sponsor Name : **Multidisciplinary Association for Psychedelic Studies** | Country: USA

	Form	Route	Medicinal Ingredients	Strength / Unit	Basic Unit	F#
1	CAP	ORL	UNASSIGNED	12.5 mg	CAP	1
2	CAP	ORL	UNASSIGNED	20 mg	CAP	**2**
3	CAP	ORL	UNASSIGNED	62.5 mg	CAP	**3**
4	CAP	ORL	UNASSIGNED	125 mg	CAP	**4**

Comparator Product: Active Placebo (Low Dose MDMA + Lactose)

Screening Officer's Comment(s):
- IB (December 2007)

Previous related submission, CTA <control#>, reviewed by: N/A

Dalia Haddad
Dalia Haddad-Screening Officer

2008.12.22 / 2008.12.24
Screening start date / Completion date

Dr. Beda Vichnevsky
Assessment Officer

for 05/09 / 30h
Assigned date / Review Hours

.esponse to Clarifax
Posted by Dalia Haddad
Submission Screening Officer, Submission Management Unit
Office of Clinical Trials, Therapeutic Projects Directorate,
5th Floor, Holland Cross, Tower B
3015A
1600 Scott Street
Ottawa, Ontario
Canada K1A 0K9
Tel: 613-948-8274
Fax: 613-946-7996
dalia_haddad@hc-sc.gc.ca

December 23, 2008

This information is prepared in response to Clarifax issued to Rick Doblin on Dec 22, 2008 for a Clinical Trial Application for a study with the drug substance (product) MDMA.
Protocol Number: MP-4
Control Number: 126833

Dear Ms. Dalia Haddad,

Please find the answers to your queries below:

Excerpt from the Clarifax sent to Rick Doblin on 22 Dec 2008

1. It is mentioned that the MDMA and the active Placebo will be encapsulated. Please provide information on the following:
   - The type of capsules used
   - Brief description on the encapsulating process
   - Are the capsules BSE/TSE free?
   - Where will the encapsulating taking place?

Responses to each query are listed below.

- Capsules will be 00 opaque gelatin capsules.

- The principal investigator will transport the MDMA [redacted] will encapsulate experimental and active placebo doses of MDMA at [redacted]. The pharmacy will supply the capsules and lactose. MDMA will be weighed out (calculated as the weight of the hydrochloride salt) into gelatin capsules in combination with lactose, used to ensure that all 108 capsules have equivalent weights. All capsules will contain the exact weight of MDMA for each appropriate dose (12.5 mg (X15), 25 mg (X15), 62.5 mg (X39) or 125 mg (X39) and a varying amount of lactose to maintain equal weights.

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Deleted: between active placebo and experimental dose capsules.The study will enroll eight people in the experimental dose condition and four people in the active placebo condition, and all four of these participants may enroll in an open-label study segment. Assuming one drop-out in each condition, the study will require 15 capsules with 12.5 mg MDMA, 15 capsules of 25 mg MDMA, 27 capsules with 62.5 mg MDMA, 27 capsules with 125 mg MDMA and, for open-label sessions, 12 capsules with 62.5 mg MDMA and 12 capsules with 125 mg MDMA.

Deleted: The 12 subjects in the study will require X capsules with 12.5 mg MDMA, X capsules with 25 mg MDMA, X capsules of 62.5 mg MDMA and X capsules of 125 mg MDMA. These numbers assume all 4 subjects randomized initially to the low dose/placebo group enter into the open-label Stage 2 with full dose MDMA, and that there are two drop-outs, one from the full dose MDMA group and one from the low dose/placebo group.

The pharmacist will place capsules into numbered bottles, three capsules of the same dose per bottle. The bottles will be returned to the principal investigator, who will store all capsules in accordance with provincial and national regulations pertaining to the use of controlled substances in Canada. Each participant will be assigned capsules from one bottle for initial doses and one for supplemental doses.

The study will employ a blinded adaptive randomization procedure that uses a list of randomly generated numbers from 1 to 100 and a condition assignment to each number that maintains the 66%/33% ratio of condition assignment. A randomization monitor supervises the randomization and generates and maintains the list. When a person is enrolled, Dr. Pacey contacts the randomization monitor, the randomization monitor selects a number from amongst a set of cards based on the list, and that number is the bottle number used for that participant.

- Yes, the lactose and gelatin capsules will be BSE/TSE free.
- The encapsulation will take place at . Encapsulation will be performed by in the presence of the principal investigator, who will possess the appropriate license.

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If you need any additional information, please let me know and I will be glad to provide it

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Sincerely,

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Rick Doblin, Ph.D.
MAPS President

Health Canada Santé Canada

Therapeutic Products Directorate
5th Floor, Holland Cross, Tower B
Address Locator# 3105A
OTTAWA, Ontario
K1A 0K9

Your file *Votre référence*

Our file *Notre référence*

24 December 2008

9427-M2544-21C

Rick Doblin, Ph.D.
President, MAPS
Multidisciplinary Association for Psychedelic Studies
3 Francis Street
BELMONT, MA
USA 02478-2218
617-484-87711

ACKNOWLEDGEMENT CLINICAL TRIAL APPLICATION
RE: PROTOCOL# M-P4

Dear Dr. Doblin:

This will confirm the receipt of your complete application on December 24, 2008, regarding your information and material to support a Clinical Trial Application (CTA) for **MDMA**, control number **126833**. You are requested to refer to the file number and control number in any communication relating to this application.

Please note that additional information may be requested during the review stage.

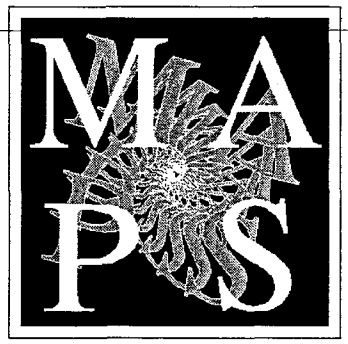
You are reminded that under paragraph C.05.006 (1) (b) of the Food and Drug Regulations, the sale of a new drug for clinical testing is prohibited if, within 30 days after the date of receipt of the complete submission, the Director has sent a notice by registered mail that the Clinical Trial Application is not satisfactory.

Yours sincerely,

Dalia Haddad
Submission Screening Officer
Office of Clinical Trials

DH/mh

Canada



December 18, 2008

Dr. John Patrick Stewart
Acting Director,
Office of Clinical Trials
Therapeutic Products Directorate
5th Floor, Holland Cross, Tower B
Address Locator: 3015A
1600 Scott Street
Ottawa, Ontario
Canada K1A 0K9

Dear Dr. Stewart,

Enclosed is a Clinical Trial Application (CTA) for a Phase 2 study entitled, "A Randomized, Active Placebo-controlled Pilot Study of 3,4- methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD)-Canada." The principal investigator for the study is Dr. Ingrid Pacey MB BS FRCP[C], Vancouver, British Columbia. The enclosed forms, investigator's brochure, protocol, consent materials and chemistry information are presented for review for this CTA. This protocol and associated informed consent have already been reviewed and approved by IRB Services, Aurora, Ontario, Canada.

The sponsor of the study is the Multidisciplinary Association for Psychedelic Studies (MAPS), a US-based non-profit research and educational organization working to develop MDMA into a prescription medicine for use in combination with psychotherapy. The enclosed application is for an investigation that is part of an international series of Phase 2 studies, the protocols of which have all been submitted to FDA as part of MAPS IND #63-384. MAPS has successfully completed an MDMA/PTSD pilot study in the US in 21 subjects and is sponsoring ongoing MDMA/PTSD studies in Switzerland and Israel, each to enroll 12 subjects and estimated to be completed around the end of 2009. Our Canadian MDMA/PTSD is an attempt to replicate our US results. Our Canadian MDMA/PTSD is an attempt to replicate our US results.

Multidisciplinary Association for Psychedelic Studies
MAPS • Rick Doblin • 3 Francis Street • Belmont, MA. 02478-2218 •
617 484-8711, Fax: -8427 • www.maps.org • rick@maps.org

MAPS has also helped to initiate a study of MDMA-assisted psychotherapy for people with anxiety related to a cancer diagnosis, taking place at McLean Hospital, Harvard Medical School.

I look forward to hearing from you regarding the results of your review.

Sincerely

Rick Doblin

Rick Doblin PhD
President, MAPS

Multidisciplinary Association for Psychedelic Studies
MAPS • Rick Doblin • 3 Francis Street • Belmont, MA. 02478-2218 •
617 484-8711, Fax: -8427 • www.maps.org • rick@maps.org

Health Canada / Santé Canada

Therapeutic Products Directorate
5th Floor, Holland Cross, Tower B
Address Locator# 3105A
OTTAWA, Ontario
K1A 0K9

SEP 0 3 2013

9427-M2544-21C

Your file / Votre référence

Our file / Notre référence

Clinical Research
Multidisciplinary Association for Psychedelic Studies
1215 Mission St.
SANTA CRUZ, CA
95060 USA

No Objection Letter RE: Amendment # 1 to Protocol # MP-4 (Version 2) and Quality Amendment

Dear

This is to advise you that the data concerning your Clinical Trial Application for **MDMA**, control number **167090** which were received on August 8, 2013, have been reviewed and we have no objection to the amendment to the study. Please note that a new control number has been assigned to this Clinical Trial Application Amendment only. Any correspondence relating to the original CTA should be referenced to the original control number assigned. I would remind you of the necessity of complying with the *Food and Drug Regulations*, Division 5, in the sale of this product for clinical testing. In addition, the regulations impose record keeping responsibilities on those conducting clinical trials. You are also reminded that all clinical trials should be conducted in compliance with the Therapeutic Products Directorate's *Guideline for Good Clinical Practice.*

Please note that Health Canada has implemented electronic reporting of adverse drug reactions and is currently in pilots with some sponsors. Those sponsors who have an established electronic connection with Canada Vigilance Production stream should submit their reports using the distribution rules provided to them by Health Canada, and reporting to multiple directorates is no longer required. For the sponsors who have not yet established this connection, they should continue submitting their reports to the applicable directorate by fax or by courier. The following website provides further clarification on Health Canada's adverse drug reactions reporting requirements for clinical trials: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/prodpharma/applic-demande/guide-ld/ich/efficac/e2a_pre_notice_avis-eng.pdf

Consistent with Health Canada's Notice - *Registration and Disclosure of Clinical Trial Information* of November 30, 2007, sponsors are encouraged to register their clinical trials within 21 days of the trial's onset, using a publicly available registry that conforms with international standards for registries such as: Clinicaltrials.gov (www.clinicaltrials.gov); Current Controlled Trials (www.controlled-trials.com).

Should you have any questions concerning this letter, please contact the Office of Clinical Trials (613) 941-2132.

Yours sincerely,

Lisa Carter for

Léo Bouthillier, Ph.D.
Manager - Clinical Trials Group II
Office of Clinical Trials

LB/en

Canada

Sponsor: **Multidisciplinary Association for Psychedelic Studies (MAPS)**
Protocol Title: "**A Randomized, Double-Blind, Dose Comparison Phase 2 Pilot Study of Manualized 3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD) – Canada**"
Protocol Number: MP-4
Health Canada File#: **9247-M2554-21C** Health Canada Control#: **127822**
July 31, 2013

CTA-A

Multidisciplinary Association for Psychedelic Studies
1215 Mission Street, Santa Cruz, CA 95060 USA
Phone: +1 (831) 429-6362 Fax +1 (831) 429-6370

July 31, 2013

Office of Clinical Trials
Therapeutic Products Directorate
Health Canada
5th Floor, Holland Cross, Tower B
Address Locator: 3105A
1600 Scott St.
Ottawa
Ontario K1A 0K9
Canada

Re: **Study #MP-4** "A Randomized, Double-Blind, Dose Comparison Phase 2 Pilot Study of Manualized 3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD) – Canada"
Health Canada File#: **9247-M2554-21C** Health Canada Control#: **127822**

Dear Office of Clinical Trials, Therapeutic Products Directorate

Please find along with this letter a clinical trial application amendment for the study listed above, Control number 127822. The amendment application consists of the following documents, in order and listed in a table of contents:

1.1 Table of Contents
1.2 Application Information
- 1.2.1 Drug Submission Application Form (HC/SC 3011)
- 1.2.3 Investigator's Brochure
- 1.2.5 Study Protocols
  - 1.2.5.1 Amendment 1 Version 2 Summary of Changes
  - 1.2.5.2 Amendment 1 Version 2 Synopsis and Protocol
  - 1.2.5.3. Most recently authorized protocol
- 1.2.6 Informed Consent Documents
  - 1.2.6.1 REB Approval and Letter of Attestation
  - 1.2.6.2 Version 2 Main Consent
  - 1.2.6.3 Version 3 Video Consent
- 1.2.7 Clinical Trial Site Information

[1.3] Electronic Information (to be contained on a compact disc mailed along with this letter]

Multidisciplinary Association for Psychedelic Studies
1215 Mission Street, Santa Cruz, CA 95060 USA
Phone: +1 (831) 429-6362 Fax +1 (831) 429-6370

Please do not hesitate to call me if you have any further questions.

Thank you very much for your assistance,

Sincerely,

[redacted] Clinical Research

Drug Submission Application

Part 1 - Manufacturer/Sponsor and Drug Product Information

Health Canada Use Only: 1. Submission No.	2. Responsible Area	3. File No.	4. Date of Receipt YYYY MM DD

5. Type of Submission	6. Number of Volumes / Compact Discs	7. Schedule
Clinical Trial Application – Amendment	1	Schedule III

8. Brand or Proprietary or Product Name (should be the same as the brand name on the product label):
None

9. Proper, Common or Non-Proprietary Name : 3,4-methylenedioxymethamphetamine (MDMA)

A) Manufacturer/Sponsor (In cases where a DIN/Notice of Compliance (NOC) is issued, this will be the DIN/NOC Owner) (For CTA, CTA-A, VIND and VIND-AM, refer to attached Guidance)

10. Company Code	11. Manufacturer/Sponsor Name (Full Legal Name - No Abbreviations):
MAPS	Multidisciplinary Association for Psychedelic Studies

12. Street/Suite	13. City/Town	14. Prov./State	15. Country	16. Postal/ZIP Code
1215 Mission St.	Santa Cruz	CA	USA	95060

Contact Person for Manufacturer/Sponsor (In cases where a DIN/NOC is issued, this is the DIN/NOC Owner contact)

17. Name	18. Telephone No.	19. Fax No.	20. Language Preferred
		831-429-6370	X English

21. Title	22. E-mail
Clinical Research	@maps.org

B) Contact for THIS Drug Submission

23. Company Name (Full Name - No Abbreviations)
Multidisciplinary Association for Psychedelic Studies

24. Street/Suite/Post Office Box	25. City/Town :	26. Prov./State	27. Country	28. Postal/ZIP Code
1215 Mission St.	Santa Cruz	CA	USA	95060

29. Name	30. Telephone No.	31. Fax No.	32. Language Preferred
		831-429-6370	X English

33. Title	34. E-mail
Clinical Research	@maps.org

C) Regulatory Mailing Address (Complete where a DIN is to be issued, refer attached Guidance) **Same as A Above**

35. Company Name (Full Name - No Abbreviations)
Same as above

36. Street/Suite/Post Office Box	37. City/Town	38. Prov./State	39. Country	40. Postal/ZIP Code

Regulatory Mailing Contact **Same as A Above**

41. Name	42. Telephone No.	43. Fax No.	44. Language Preferred
Same as above			X English

45. Title	46. E-mail

D) Canadian Importer (Complete ONLY where Address in A is not in Canada. EXCEPTION for CTAs, see footnote)[1] **Same as C Above**

[1] For clinical trial applications (human drugs), if clinical trial drugs are to be imported into Canada, importers should be authorized by the sponsor, **regardless of the sponsor's location**. Appendix 1 should be completed and submitted for each importer in Canada. Canadian importer(s) must be located within Canada. Refer to the attached guidance and the "Guidance for Clinical Trial Sponsors" for roles and responsibilities.

47. Name of Importer (Full Name - No Abbreviations) Colin Holyk, Kerrisdale Pharmacy				
48. Street/Suite/Post Office Box 5591 West Blvd	49. City/Town Vancouver	50. Province BC	51. Country CANADA	52. Postal Code V6M 3W6

E) Address to which the Drug Notification Form (DNF)/NOC are to be sent: **Same As Above: A: X B: C: D:**

53. Related Submissions (referred to in this submission):

A) Type	Control No.	Brand Name	Manufacturer/Sponsor Name	File No.	Date Cleared

Associated DIN(s) :

Reason for Submission:

Attach separate sheets (same format) if necessary. Number of pages attached: _____

Part 2 - Drug Product Formulation Information

54. Proposed Shelf Life 20 years 0 months at 22 °C.

55. Country(ies) of Manufacture: Switzerland

56. Medicinal (Active) Ingredient(s) - If the ingredient was sourced from Animal/Human, complete and submit Appendix 4.

CAS No. (if applicable)	Ingredient Name	Standard	Strength	Units	Per	Calculated as Base?		Animal/ Human Source	
	3,4-methylenedioxymethamphetamine	USP	125	mg	capsule	☐ Yes	X No	☐ Yes	X No
	Same as above	USP	100	mg	capsule	☐ Yes	X No	☐ Yes	X No
	Same as above	USP	62.5	mg	Capsule	☐ Yes	X No	☐ Yes	X No
	Same as above	USP	50	mg	capsule	☐ Yes	X No	☐ Yes	X No
	Same as above	USP	12.5	mg	Capsule	☐ Yes	X No	☐ Yes	X No
	Same as above	USP	25	mg	capsule	☐ Yes	X No	☐ Yes	X No

57. Non-medicinal Ingredient(s) - If the ingredient was sourced from Animal/Human, complete and submit Appendix 4.

For formulation variations pertaining to the same DIN (for example [e.g.] multiple flavourings, colours, fragrances), fill out the variant name and list all the non-medicinal ingredients for each variant type.

Variant Type [if applicable]: _____

CAS No. (if applicable)	Ingredient Name	Standard	Strength	Units	Per	Animal/ Human Source	
	A) Preservatives						
						☐ Yes	☐ No
						☐ Yes	☐ No
	B) Colouring Agents						
						☐ Yes	☐ No
						☐ Yes	☐ No
	C) Other[2]						
	Lactose		12.5-150	mg	capsule	X Yes	☐ No
						☐ Yes	☐ No
	D) Capsule Shell Ingredients (if applicable)						
	Gelatin		1		capsule	X Yes	☐ No
						☐ Yes	☐ No

[2] For products regulated solely by Division 1: state the purpose of any non-medicinal ingredient(s) included under "Other"

58. Animal and/or Human Sourced Material(s) Used at Any Stage in the Manufacture of the Drug - If the material was sourced from Animal/Human, complete and submit Appendix 4.

CAS No. (if applicable)	Material Name	Standard	Present in Final Container	
			☐ Yes	☐ No
			☐ Yes	☐ No

59. Is any ingredient listed under Section 56 or 57 a Nanomaterial? [X] No

If Yes, provide the name of the ingredient:

60. Dosage Form: white, crystalline powder

61. Container Type Clear uncoloured gelatin capsules Package Size : 03

62. Therapeutic/Pharmacological Classification : Monoamine releaser and uptake inhibitor; Entactogen

63. Route(s) of Administration: Oral

64. Drug Product 9 Biologic / Radiopharmaceutical [X] Pharmaceutical Disinfectant Drug and Medical Device

65. Drug Use [X] Human [9 Paediatric (0-18 years of age) Adult] Radiopharmaceutical Veterinary
Disinfectant [Hospital Food Processing Medical Instruments Domestic Barn Institutional/Industrial Contact Lens]

66. Is this a Non-prescription drug to which one or more Schedule A claims apply? Yes [X] No

If Yes, complete and attach the Schedule A Form (Appendix 5).

67. Proposed Indication/Use: Facilitating psychotherapy for the treatment of Post-Traumatic Stress Disorder

68. Proposed Dosage (by age / species - include maximum daily dose)

Full dose condition:125mg +62.5mg at t+1.5-2.5h Min 125mg, max 187.5mg

Comparator dose condition: 50mg + 25mg at t+1.5-2.5h Min 50mg, max 75mg

Open-label titration (Stage 2): 100mg to 125mg + 50mg to 62.5mg at 1.5-2.5h Min 100mg, max 150mg

69. Draft of Proposed Canadian Labels (inner and outer) enclosed? Yes [X] No Package Insert enclosed? Yes [X] No

For CTAs, CTA-As, VINDs and VIND-AMs labels should not be submitted unless requested by the appropriate Directorate.

70. Rationale for all SNDS, SANDS, (all human drug types); Veterinary Supplemental New Drug Submission (VSNDS), Veterinary Supplemental Abbreviated New Drug Submission (VSANDS) (all veterinary drug types); or for biological drug DIN submissions

☐ New route of administration, dosage form and/or strength
☐ New claims/use, indications, recommended administration or dosage regime
☐ Change in formulation or method of manufacturing with clinical/bio data
☐ Change in drug substance/product (site, method, equipment, process control)
☐ Replace sterility test with process parametric release
☐ Confirmatory studies
☐ Other (please specify): _____

on a separate attached sheet.

Complete Sections 72 - 74 for Veterinary Products only

72. Species and Subtypes Recommended for use	73. Used for treatment of food-producing animals? 9 Yes 9 No		
	74. Withdrawal Time Species	Days	Hours

I, the undersigned, certify that the information and material included in this drug submission application is accurate and complete[3].

75. Name of Authorized Signing Official	76. Signature	77. Date YYYY MM DD
		2013 07 23
78. Title Director of Clinical Research	no.	80. Fax No. (831) 429-6370
81. Name of Company to which the Authorized Signing Official Belongs		

[3] If the signing official is a third party acting on behalf of the manufacturer/sponsor identified in section 11, a letter of authorization, signed by the manufacturer/sponsor (section 11), must be filed with the completed submission application form (see Appendix 2).

Appendix 1 - for Clinical Trial Applications and Amendments only

Template Authorisation for a Third Party to Import the New Drug Described in this Clinical Trial Application or Amendment[4]

I, _____ authorize Colin Holyk of Kerrisdale Pharmacy

(list each applicable importer [name and address],

_____

add more space as necessary or attach a list of importers)

attached list of importers ☐ Yes ☒ No

to import the new drug for the purposes of the clinical trial described within this application.

Signed: _____

Print name: _____

Title: Clinical Research

Clinical Trial Sponsor: Multidisciplinary Association for Psychedelic Studies

Date: 7/23/13

[4] Submit with application if the clinical trial sponsor is authorizing one or more third parties to import the new drug for the purposes of the clinical trial described within this application. An authorisation is required for each clinical trial application. As additional importers are identified, additional copies of Appendix 1 should be provided to Health Canada. If the importer has not changed when a clinical trial application amendment is filed, Appendix1 does not need to be re-submitted.

Health Canada *Form HC-SC 3011*

Appendix 3 - Clinical Trial Application Information (for Clinical Trial Applications for human drugs only)

82. Clinical Trial Protocol Number (must be assigned)	83. Clinical Trial Protocol Title
control number 127822	A Randomized, Active Placebo-controlled Pilot Study of 3,4- methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD) - Canada

84. Is the investigational product obtained from the Canadian market?

☐ Yes DIN(s):_____

☒ No Country(ies) obtained: Switzerland

85. Anticipated Clinical Trial Composition (check all that apply):	86. Phase of Clinical Trial (check appropriate box):
☐ Paediatric population (0-18 years of age)	☐ Phase I - bioequivalence study (7-day administrative target)
☐ Females ☐ Males	☐ Phase I - study in healthy humans (30-day default)
☒ Adult population	☐ Phase I - other (30-day default)
☒ Females ☒ Males	☒ Phase II (30-day default)
	☐ Phase III (30-day default)
	☐ Other (please specify): _____

87. Information regarding Research Ethics Board that has refused to approve the protocol and/or informed consent form enclosed?

☐ Yes ☒ No ☐ N/A ☐ Not known at this time

88. Clinical Trial Site Information Form enclosed for all sites known at time of application?

☒ Yes ☐ No ☐ No sites are known at this time

In respect of the clinical trial identified in Appendix 3 of this Drug Submission Application form we certify that:

1. The information and material contained in, or referenced by, this application are complete and accurate and are not false or misleading.
2. If requested by Health Canada, additional information or samples required to assess this application will be provided within two calendar days following receipt of the request from Health Canada.
3. The clinical trial will be conducted and the drug used in accordance with the protocol and the requirements set out in Division 5 of the *Food and Drug Regulations*. The clinical trial will be conducted in accordance with good clinical practices.
4. The trial or amendment will not commence at any site until receipt of a No Objection Letter from the Therapeutic Products Directorate or the Biologics and Genetic Therapies Directorate of Health Canada, or the elapse of 30 calendar days following receipt of the complete application by Health Canada, whichever comes first, and the receipt of the Research Ethics Board Approval.
5. Records will be maintained for a period of 25 years and will be accessible for on-site inspection by Health Canada Inspectors.

89. Senior Medical Officer or Scientific Officer in Canada	90. Tel. No. and Address	91. Signature	92. Date
Ingrid Pacey MBBS FRCP[C]	604-732-9309 2364 Wyatt Ave Vancouver BC	[redacted]	YYYY MM DD 2013 07 23
93. Senior Executive Officer	**94. Tel. No.**	**95. Signature**	**96. Date**
[redacted]	831-429-8362	[redacted]	YYYY MM DD 2013 07 23

MAPS
MULTIDISCIPLINARY ASSOCIATION FOR PSYCHEDELIC STUDIES

INVESTIGATOR'S BROCHURE

SPONSOR: Multidisciplinary Association for Psychedelic Studies

PRODUCT: 3,4-methylenedioxymethamphetamine (MDMA)

IND #: 63,384

EDITION: 7th Edition

RELEASE DATE: August 1, 2013

REPLACES: 6th Edition, dated September 7, 2010

1. Table of Contents

2. List of Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
AE(s)	Adverse Event(s)
ALT/SGPT	Alanine aminotransferase
AMI	Acute Myocardial Infarction
AST/SGOT	Aspartate aminotransferase
BDI-II	Beck Depression Inventory II
C	Celsius
CAPS	Clinician Administered PTSD Scale
CNS	Central Nervous System
CPK	Creatine Phosphokinase
CRA	Clinical Research Associate
CRF(s)	Case Report Form(s)
C-SSRS	Columbia Suicide Severity Rating Scale
DEA	Drug Enforcement Administration
DBP	Diastolic Blood Pressure
DMF	Drug Master File
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders - IV
EKG	Electrocardiogram
EMDR	Eye Movement Desensitization and Reprocessing
EMEA	European Medicines Agency
ESR	Erythrocyte Sedimentation Rate
EU	European Union
FDA	Food and Drug Administration
GAF	Global Assessment of Functioning
GCP	Good Clinical Practice
HCl	Hydrochloride
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
ISF	Investigator Site File
IV	Intravenous
EMEA	European Medicines Agency
LD50	Lethal dose in 50% of cases
LSD	d-lysergic acid diethylamide
MAOI	Monoamine oxidase inhibitor
MAPS	Multidisciplinary Association for Psychedelic Studies
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MDMA	3,4-methylenedioxymethamphetamine
MP-1	Sponsor's first Phase 2 clinical trial of MDMA-assisted psychotherapy for PTSD

PRN	As needed
PT	Prothrombin Time
PTCA	Percutaneous Transluminal Coronary Angioplasty
PTSD	Posttraumatic Stress Disorder
PTT	Partial Thromboplastin Time
RBC	Red Blood Cell Count
RDW	Red Cell Distribution Width
RRPQ	Reactions to Research Participation Questionnaire
SAE(s)	Serious Adverse Event(s)
SBP	Systolic Blood Pressure
SCID	Structured Clinical Interview for Diagnoses
SERT	Serotonin Transporter
SL	Sublingual
SNRI	Selective Serotonin and Norepinephrine Uptake Inhibitor
SOP(s)	Standard Operating Procedure(s)
SSRI	Selective Serotonin Reuptake Inhibitor
SUD	Subjective Units of Distress
TSH	Thyroid Stimulating Hormones
U.S.	United States of America
WBC	White Blood Cell Count

3. Summary

The Multidisciplinary Association for Psychedelic Studies (MAPS) is a U.S.-based non-profit research and educational organization supporting research of the therapeutic potential of MDMA (3,4-methylenedioxy-N-methylamphetamine). MAPS is sponsoring clinical trials to test medical uses of MDMA-assisted psychotherapy for patients with chronic disorders such as Posttraumatic Stress Disorder (PTSD), social anxiety related to autism, pain and anxiety related to terminal illnesses and further research into its potential for therapeutic applications. MDMA-assisted psychotherapy is an innovative mode of treatment that combines psychotherapeutic techniques with the administration of MDMA, a pharmacological adjunct that enhances certain aspects of psychotherapy. This Investigator's Brochure (IB) describes the physical, chemical, and pharmacological characteristics of MDMA, its effects in nonclinical and clinical studies, and the safety profile of MDMA-assisted psychotherapy. This IB focuses on research and information relevant to researchers and regulators engaged in clinical trials with MDMA.

MDMA is a ring-substituted phenethylamine that produces anxiolytic and prosocial effects through release of the monoaminergic neurotransmitters with the greatest effect on serotonin, followed by norepinephrine and dopamine. MDMA has been shown to acutely decrease activity in the left amygdala and increase blood flow to the prefrontal cortex in the brain. MDMA has also been found to increase serum levels of the neurohormones oxytocin and arginine vasopressin in humans, which are likely to be involved in increased trust and attenuated reactivity to threatening cues. The combined neurobiological effects of MDMA can increase compassion for self and others, reduce defenses and fear of emotional injury, while enhancing communication and capacity for introspection. These factors taken together can provide the opportunity for a corrective emotional experience in the context of psychotherapy. Many of the therapeutic effects of MDMA-assisted psychotherapy are evident within a short period of treatment, often after the initial session. Increased feelings of interpersonal closeness, changes in social perception and reduced anxiety may make MDMA a suitable pharmacological adjunct to enhance psychotherapy for anxiety disorders such as PTSD and possibly social anxiety more generally. MDMA may provide a much-needed option in the treatment of PTSD and other conditions associated with anxiety.

A substantial amount of data, both clinical and nonclinical, has been collected over nearly a century of research on the physiological and psychological effects of MDMA in humans and animals. Estimates from animal data suggest a LD50 in humans between 10 - 20 mg/kg [1]. Due a wide range of responses to identical milligram per kilogram (mg/kg) dosing [2], possibly as a result of inconsistent relationship between body weight and pharmacodynamic activity, the sponsor's human trials use fixed doses that are equivalent to between 1 and 2 mg/kg (active doses in studies range from 75mg to 187.5mg) to achieve a more consistent response between subjects. The pharmacokinetics of MDMA in humans have been characterized using oral doses of up to 150 mg MDMA. Onset of MDMA effects occurs 30 to 60 minutes after administration [3, 4], peak effects appear 75 to 120 minutes post-drug [2, 5-7], and duration of effects lasts from three to six hours [5, 6, 8], with most effects returning to baseline or near-baseline levels six hours after drug administration. Unexpected and expected serious adverse events involving administration of MDMA in government-approved clinical trials have been rare and non-life threatening. MDMA produces sympathomimetic effects that include significant transient, self limited increases in heart rate and blood pressure that were likely to be well tolerated by healthy

individuals [2, 4-6, 9-12]. Most people do not experience elevations that exceed those seen after moderate exercise. In the first MAPS Phase 1 safety study, MDMA was found to cause a significant increase in body temperature and heart rate in some healthy volunteers [13]. However, these increases were found to be transient and tolerable in a controlled clinical setting. Risks posed by elevated blood pressure are addressed in clinical trials by excluding people with pre-existing uncontrolled hypertension and by frequently monitoring blood pressure and pulse. Common reactions reported in clinical trials are transient and diminish as drug effects wane during the session and over the next 24 hours. The effects include lack of appetite, insomnia, dizziness, tight jaw or bruxism, difficulty concentrating, impaired gait or balance, dry mouth, ruminations, muscle tension and thirst. Less common reactions include restlessness, parasthesias, impaired judgment, perspiration, drowsiness, and nystagmus. While anxiety, headache, fatigue, insomnia and lack of appetite were reported by 40% to 80% of subjects in both placebo and MDMA conditions in MAPS study MP-1 (N=23), tight jaw, nausea, impaired gait/balance, and sensitivity to cold were more often reported by subjects in the MDMA than the placebo condition. MDMA may produce modest changes in immune functioning, lasting up to 48 hours. Because of their limited duration, these changes are not likely to have clinical significance beyond several days of possible increased risk of viral upper respiratory infection or similar illness. MDMA was administered to thousands of people prior to scheduling and millions continue to use ecstasy around the world in various non-medical settings [14-18]. While a number of serious adverse events, including fatalities, have been reported after non-medical ecstasy and poly-drug use in unsupervised and uncontrolled settings, these events are relatively rare given the prevalence of ecstasy use [19, 20]. The common effects in ecstasy and poly-drug use include hyperthermia, psychiatric problems, hepatotoxicity, and hyponatremia. Currently MDMA has been administered to over 850 individuals for research purposes without the occurrence of unexpected drug-related Serious Adverse Events.

To date in the MAPS clinical research program there have been 79 people exposed to MDMA and a total of 210 exposures. MAPS has published results showing clinically and statistically significant improvements in PTSD severity from 20 subjects treated in their first pilot study (MP-1 and MP-1 extension) in the United States (U.S.) [21]. Findings from the long-term follow-up of MP-1 subjects suggest that therapeutic benefits were sustained over an average of 41 months post-treatment [22]. The sponsor's second Phase 2 pilot study conducted in Switzerland (MP-2) in 12 subjects suggests clinically significant improvements in PTSD symptoms with a trend toward statistical significance [23]. Long-term follow-up data 12 months later suggest that therapeutic benefits continued to increase in this subject population. In addition, the sponsor supported an initial pilot study with two experimental sessions comparing full dose to 25 mg active placebo MDMA in Israel that treated five subjects, with no drug-related Serious Adverse Events (SAEs). A dose-response study of MDMA-assisted psychotherapy for PTSD enrolled six subjects, with four receiving MDMA [24] without producing any safety concerns and observing some symptom reduction.

MAPS current program consists of one Phase 1 study of MDMA-assisted psychotherapy in the U.S. and four Phase 2 MDMA/PTSD studies in the U.S., Canada and Israel that are actively recruiting. Ongoing and planned Phase 2 studies of MDMA-assisted psychotherapy for PTSD treatment are laying the groundwork for an End-of-Phase 2 meeting with FDA and Phase 3 multi-site MDMA/PTSD research studies. Based on the experience in chronic, treatment-refractory PTSD, MAPS is exploring new indications for this treatment. Due to similarities in

symptom profiles and to reports from anecdotal research, MAPS is conducting a protocol investigating changes in social anxiety experienced by autistic adults when using two sessions of MDMA-assisted therapy, interspersed with biweekly non-drug integration sessions.

4. Introduction

MDMA:3,4-methylenedioxy-N-methylamphetamine, is not a novel compound, the history of its use in humans predates controlled studies in healthy volunteers and clinical trials. MDMA was first synthesized and patented by Merck in 1912 [25], but is currently not covered by a patent. MAPS currently holds the Drug Master File and an IND for MDMA with the U.S. Food and Drug Administration (FDA). After MDMA was rediscovered by the chemist Alexander Shulgin [26], he and his colleagues provided initial reports of its pharmacology and effects in humans [27, 28]. MDMA was found to robustly influence human emotional status in a unique way [28] without adversely effecting physiological functions or perception, such as visual perception or cognition [3, 5, 7:Vollenweider, 1998 #880].

In the Merck Manual, MDMA is in the entactogen class. Entactogens contain a ring-substituted amphetamine core, and belong to the phenethylamine class of psychoactive drugs. Entactogens as a class of drugs are described as promoting acceptance and compassion for self and others, changing recognition and response to emotions and increased interpersonal closeness. In comparison to anxiolytics, antidepressants and atypical antipsychotics, MDMA does not require steady state levels in the blood to function as a catalyst to psychotherapy. A limited number of exposures to MDMA, spaced approximately a month apart at moderate doses, are sufficient to obtain comparable or better results than other medications that require daily dosing. This infrequent dosing mitigates adverse event frequency and improves the risk/benefit ratio of MDMA, which may provide a significant advantage over medications that require daily dosing.

Shulgin and Nichols were the first to report the effects of MDMA in humans [28]. MDMA-assisted psychotherapy first occurred during the mid to late 1970s after Shulgin introduced MDMA to a psychotherapist. Reported effects of MDMA include enhanced feelings of closeness to others, wellbeing, and insightfulness [29-31]. Prior to scheduling in 1985, MDMA was used in individual, couple, and group therapy to treat diverse psychological disorders, including moderate depression and anxiety [30, 32] [33, 34]. It was also found to be useful in reducing physical pain secondary to certain kinds of cancer [33]. No formal controlled clinical trials of safety and efficacy were conducted at the time [30, 35].

During the early 1980s, increasing numbers of people began using MDMA, sold as "Ecstasy" outside of therapeutic contexts [14]. The first wave of non-medical use occurred not only in dance clubs but also in groups of people who used the drug in a self-exploratory or spiritual context. Non-medical use continues today in the same contexts [17, 36].

MDMA was added to the list of Schedule I controlled substances in the U.S. in 1985, indicating that it has a high potential for abuse and no accepted medical use [37, 38]. Shortly after it was scheduled, animal studies described long term decreases in markers of serotonergic functioning after high or repeated doses of MDMA administration [39] that were not relevant to doses in clinical trials. A recently published meta-analysis took careful steps to overcome methodological limitations in previous work, and found only modest evidence of neurotoxicity [40]. Reports of

adverse events seen following ecstasy use [41-43] and cognitive, physiological, and imaging findings in humans raised concerns regarding the safety of MDMA administration [44-48]. Preclinical studies have often employed inappropriately high doses of MDMA and their findings are open to several interpretations [49, 50], and the vast majority of studies of ecstasy users are retrospective reports in polydrug-using ecstasy users [40, 51]. Classification to schedule 1 combined with the early research in animals and recreational users hampered clinical research into the medical uses of MDMA until the 1990's.

While the initial studies in the 1990s examined the physiological effects of MDMA narrowly from a safety perspective, recent studies have examined the effects of this compound on attention, prosocial effects, memory and brain activity, and human drug discrimination. Findings from an initial report indicated that MDMA-assisted psychotherapy could be conducted safely in people with chronic treatment resistant PTSD[52]. In addition placebo-controlled Phase 1 clinical trials confirmed that MDMA produces an easily controlled intoxication characterized by euphoria, increased well being, sociability, self-confidence, and extroversion, transient increases in anxiety and minor alterations in perception [3, 5-7, 53-57]. In MAPS first Phase 2 study, MP-1, no difference was seen in cognitive function between placebo and MDMA groups after MDMA was given on 2 occasions a month apart in the therapeutic dose range. In addition, published results from the first two Phase 2 studies (MP-1, MP-2) showed significant durable improvements in PTSD symptoms. Based on the current state of scientific knowledge and the risk/benefit profile of therapeutic doses of MDMA, it appears favorable to pursue the research of MDMA as a medicine used as an adjunct to psychotherapy.

5. Physical, Chemical, and Pharmaceutical Properties and Formulation

MDMA is structurally similar to amphetamines and mescaline. MDMA, also known as 3,4-methylenedioxy-n-methylamphetamine and N-methyl-3,4-methylenedioxyamphetamine, has the chemical formula of $C_{11}H_{15}NO_2$. It was first synthesized as a precursor of a haemostatic drug called methylhydrastinine as a phenylisopropylamine derivative of safrole, an aromatic oil found in sassafras, nutmeg, and other plants [1].

MDMA is a chiral molecule, possessing two enantiomers, S(+)-MDMA and R(-)-MDMA, with S(+)-MDMA being more potent than R(-)-MDMA [1, 58]. All research in humans to date and the majority of nonclinical studies have used racemic MDMA, or an admixture containing equal amounts of both enantiomers. Studies of drug discrimination in rodents [59, 60] and studies of self-administered and experimenter-administered MDMA enantiomers in primates [59, 61-64]suggest that MDMA enantiomers may produce different physiological and rewarding effects, but that there may be some synergy between the two when administered as a racemate. It seems that R(-)-MDMA may have hallucinogen-like effects, compared to S(+)-MDMA, which exhibits psychomotor stimulant-like effects. Findings comparing the effects of the enantiomers of the related compound methylenedioxyethylamphetamine (MDE) suggest that these different effects of MDMA enantiomers may occur in humans [65]. According to an *in vivo* microdialysis study, S(+)-MDMA may be associated with greater dopamine release in specific brain areas [66]. A recent study in monkeys found that S(+)-MDMA, but not R(-)-MDMA, significantly increased extracellular dopamine levels in the dorsal striatum, whereas S(+)-MDMA significantly increased serotonin levels [63]. MDMA available for human in clinical trials is racemic, containing roughly equal amounts of both enantiomers. Any differential effects of the

enantiomers remain untested in humans.

For clinical trials, the Sponsor used recemic MDMA from two sources. Studies in the United States use MDMA manufactured in 1985 by David Nichols, Ph.D., at the Department of Medicinal Chemistry and Pharmacology, Purdue University, West Lafayette, IN. The MDMA supply for the Sponsor was manufactured as a single lot for use in federally approved clinical research and has been utilized by a number of investigators in the U.S. A stability analysis conducted in 2006 indicates that the compound remains highly stable and pure after 21 years of storage [67]. Studies conducted outside of the U.S. use MDMA from a single batch manufactured in 1998 by Lipomed AG in Arlesheim, Switzerland and maintained by Prof. The most recent analysis of drug stability and purity conducted on February 2, 2010 confirmed that this MDMA is 99.9% pure with no detectable decomposition. For Sponsor-supported studies, MDMA in the form of white crystalline powder is compounded with inert material into capsules. The capsules are stored in sealable containers placed within a dark safe at ambient temperature. Capsules are administered orally with a glass of water. Details of manufacturing are available from the manufacturers upon request.

MDMA doses in sponsor-supported studies are fixed, rather than based on body weight due to evidence of non-linear metabolism. Full dose is 125 mg, which is equivalent to 1.25 mg/kg (100kg) to 2.6 mg/kg (48kg) for the initial dose. The optional supplemental dose of 62.5 mg is equivalent to 1.3 mg/kg (100kg) to 2.6 mg/kg (48kg). Various comparator doses of less then 125mg of MDMA are also used in the clinical trials.

6. Nonclinical Studies

6.1. Nonclinical Pharmacology

MDMA possesses a complex pharmacological profile that is dominated by its effects as a monoamine releaser and reuptake inhibitor. MDMA prevents the uptake of serotonin (5-HT), norepinephrine (NE), and dopamine (DA) and is involved in the release of these three neurotransmitters, with the greatest effects on serotonin release. Receptor binding studies of MDMA employing to very large amounts of MDMA relative to human plasma Cmax found some affinity for specific serotonin, norepinephrine, acetylcholine, and histamine receptors, reporting that strength of activity on these receptors is low in comparison to monoamine transporters [68-71]. *In vitro* studies suggest that MDMA inhibits norepinephrine uptake more strongly than dopamine uptake [72, 73] and that MDMA does not have as strong an affinity for the dopamine transporter as methamphetamine [74]. MDMA appears to alter the conformation of the serotonin transporter, enabling serotonin to diffuse out of the neuron rather than actively transporting extracellular serotonin into these neurons [75-77]. A recent microdialysis study of a therapeutically relevant dose of MDMA in rats confirms elevated brain serotonin [78]. In combination with other drugs, or at high doses, MDMA may provoke serotonin syndrome, a suite of specific signs and symptoms that can require intervention [79-81]. Participants in sponsor-supported studies are tapered off psychiatric medications that would increase this risk.

6.2. Pharmacology and Product Metabolism in Animals

6.2.1. Pharmacology in Animals

Research into the pharmacological, physiological, or psychological effects of MDMA began in the 1950s, when the U.S. Army administered MDMA to guinea pigs, monkeys, mice, rats, and dogs as part of a military research program, possibly intended to develop chemical incapacitants or means of enhancing interrogation [82]. Investigations of the pharmacology, functional effects, and toxicity of MDMA in animals have generally included injections of large and often repeated doses of MDMA in an attempt to produce human-equivalent doses [83]. Recent reports re-examining these effects have questioned the applicability of interspecies scaling models for MDMA, and have supported nonlinear pharmacology [49, 84, 85]. A study directly comparing MDMA pharmacokinetics in humans and monkeys found that the two species metabolized MDMA in a similar but not identical manner and that MDMA had a shorter half-life in monkeys than in humans. Both species exhibited nonlinear pharmacokinetics, and it appears that monkeys and humans exhibit similar plasma MDMA levels after receiving the same dose of MDMA [86, 87]. An investigation in rats also demonstrated nonlinear pharmacokinetics in that species as well, finding that human-equivalent doses of MDMA in rats are close to or identical to those in humans and drug half-life is rapid [49]. Doses of 10 mg/kg but not 2 mg/kg produced signs of serotonin syndrome in rats, but neither dose reduced total serotonin levels in the brain two weeks after drug administration. These discoveries suggest that toxicological and behavioral studies of MDMA used doses exceeding human equivalent doses. As a consequence, it is difficult to interpret the relevance of findings in nonclinical studies employing these dosing regimes.

Most effects of MDMA on brain receptors likely arise indirectly from monoamine release. For instance, MDMA may cause acetylcholine release and changes in the GABAergic systems through serotonin release and activating $5HT_4$ receptors [88, 89]. MDMA probably stimulates $5HT_{1A}$ receptors indirectly through serotonin release, though it is possible that MDMA may also act as a partial $5HT_{1A}$ antagonist in some brain areas [90]. Findings from other studies suggest that it shares qualities with $5HT_{1A}$ agonists. Early studies in rodents suggest that $5HT_{1A}$ receptors reduce anxiety and aggression [91, 92], and some drug discrimination studies suggest that the $5HT_{1A}$ agonist 8-OH-DPAT partially or fully substitutes for MDMA [93-95]. Administering a $5HT_{1A}$ antagonist attenuates the prosocial behavior of rats, measured by preference to lie adjacent to each other, possibly because it prevents elevation in oxytocin [96, 97]. At least some direct or indirect effects of MDMA on serotonin receptors may cause changes in GABA uptake in the ventral tegmental area of rats [98].

6.2.2. Gene Transcription in Animals

A number of research teams have studied the effects of MDMA on gene expression in rodents [99-102]. However, many of these reports used 10 to 20 mg/kg MDMA, and it is unlikely that these changes can be generalized to humans given lower doses. These studies report an increase in expression of genes that regulate the GABA transporter [99, 102]. Some of the increases in transcription are in genes associated with monoamine release [99]. Investigations with serotonin transporter knockout mice suggest that at least some of these changes in gene transcription are related to serotonin release [99]. Examining rat brains two weeks after repeated MDMA detected a sharp drop in serotonin gene transporter expression [103], offering an alternative to axonal

damage as an explanation for alteration in serotonergic function after repeated doses of MDMA. A recent publication found that repeated administration of MDMA at 1 or 5 mg/kg weekly for four weeks increased transcripts for $5HT_{1B}$ receptors in various brain regions and $5HT_{2C}$ receptors in the cortex and hypothalamus [104]. Increases in transcripts of genes regulating extracellular signaling in mice were also reported [105]. It appears that serotonin may play more of a significant role than dopamine in transcription-level changes [104]. Transcripts were assessed ten hours after the last of repeated MDMA administrations and it is not clear whether these changes reflect residual acute effects of the MDMA or changes related to repeated MDMA administration. In addition, changes in transcription do not always correlate with changes in proteins produced from the genes. Future studies will need to separate direct and indirect effects of MDMA on gene expression.

6.2.3. Endocrine Effects in Animals

In rats, large doses of MDMA (10 or 20 mg/kg) elevated serum corticosterone (a rodent cortisol analog) and prolactin [106-108], with elevation lasting up to four hours after dosing, and with hormone levels attenuated by a $5HT_2$ receptor antagonist. Given the large dosage used, it is unclear if this response is analogous to elevated cortisol in humans or whether it reflects a different process. A study of isolated rat hypothalamus reported arginine vasopressin (AVP) and oxytocin release after administration of MDMA and its metabolite HMMA [109]. A recent study using 1-3 mg/kg doses found that R(-)-MDMA, but not S(+)-MDMA, significantly increased prolactin levels in rhesus monkey plasma, suggesting that at least the R(-) enantiomer of MDMA can influence endocrine signaling at doses relevant for studies in humans [63]. Fluoxetine attenuated prolactin release after administration of racemic MDMA, and fluoxetine and a 5HT2A antagonist attenuated prolactin release after R-(-)-MDMA, indicating that prolactin release is associated with serotonin release and action on 5HT2A receptors by R(-)-MDMA.[64].

6.2.4. Thermoregulatory Effects in Animals

Rodents have generally been used to study the hyperthermic effects of MDMA. Given that rodents have a much smaller body mass and do not perspire, it is unlikely that thermoregulation occurs in the same way in rodents and humans [110]. Moderate and high doses of MDMA elevate body temperature and disrupt thermoregulation in rodents [76], and doses of MDMA in the 1 to 2 mg/kg range only cause a slight increase in body temperature [111]. MDMA causes susceptibility to changes in ambient temperature in rodents, with high ambient temperature significantly increasing body temperature in mice and rats, and low ambient temperatures producing hypothermia [112-114]. High doses of MDMA also produce significant elevations in body temperature in primates [84, 115, 116]. At doses closer to those humans ingest [117], monkeys exhibit only slight to moderate elevation in body temperature [118, 119]. In contrast to findings in rodents, primates are not susceptible to changes in ambient temperature when they receive MDMA, exhibiting slight to moderate increases in body temperature regardless of the temperature of the environment [117-119], though at least one study found that the ambient temperature influenced the effects of 1.5
mg/kg i. v. MDMA on body temperature in monkeys, with lower body temperatures seen in after MDMA and cool temperatures and higher body temperatures in another group given MDMA in a warm temperature [120]. It appears that findings in rodents do not extrapolate well to primates,

and studies in humans supported by the Sponsor will address the effects of moderate doses of MDMA on thermoregulation.

6.2.5. Cardiovascular Effects in Animals

In vivo assessments of cardiovascular effects of MDMA in animals detected increased sympathetic activity, as seen in humans [76]. Injections of 20 mg/kg MDMA in conscious rodents assessed by radiotelemetry found that MDMA caused a prolonged increase in blood pressure [121]. In the same study, MDMA was found to produce mild isotonic contractions of rat aorta and vas deferens vascular tissue in anesthetized rodents, but could also inhibit prejunctional contractions evoked by stimulation [121]. An injection of 2 mg/kg MDMA elevated heart rate in rabbits [122]. The researchers found that MDMA has both pressor and depressor effects, acting through adrenergic receptors [121, 123, 124]. A study in rodents suggests that norepinephrine may play a role in cardiovascular effects [125]. Given the affinity of MDMA for the norepinephrine transporter, it is possible that the cardiovascular effects of MDMA could be attributed to norepinephrine signaling in the peripheral nervous system.

6.2.6. Behavioral Effects in Animals

In rodents, doses of MDMA equivalent to human doses produce either few or no behavioral effects. However, doses of 5 mg/kg or greater have several specific behavioral effects, including increased locomotor activity, increased anxiety at moderately high doses, and decreased anxiety at higher doses [76, 126]. Rats given lower doses of MDMA exhibited increased anxiety in the elevated plus maze [127], while rats given higher doses exhibited reduced anxiety on the maze. Rats given higher doses also reduced aggressive behavior as well as social investigation. Rodents responded to very high doses of MDMA by exhibiting flat body posture, forepaw treading and an erect tail ("Straub tail"), all signs of rodent serotonin syndrome [126]. MDMA produces some repetitive behavior in rodents, but not to the same degree as psychostimulants. MDMA leads rats to walk around a cage perimeter, interpreted as an indicator of thigmotaxis, which is a sign of anxiety [76]. However, it is notable that a recent publication failed to find thigmotaxis in rats given 5 mg/kg MDMA [128]. In contrast, rhesus monkeys do not exhibit increased locomotor activity after receiving up to 2.4 mg/kg MDMA [119].

To date, no empirical investigations have been conducted on the effects of MDMA on primate social interactions. Morley and colleagues observed rat behavior after receiving 5 mg/kg MDMA, noting that this dose correlated with prosocial behavior, such as lying next to each other [96]. Recent studies conducted by the same team of researchers suggest that MDMA increases prosocial behavior in rats by elevating oxytocin in the paraventricular nucleus through 5HT1A receptor agonism, with the oxytocin increase arising from the indirect effects of MDMA on 5HT1A receptors [97, 129]. To date, there have been no human pharmacological challenge studies combining MDMA with 5HT1A agonists, while 5HT1A antagonists have negligible effects on subjective or physiological effects of MDMA in humans [57, 130-132]. As a result, it is unclear whether the rat behavior is analogous to human reports of increased feelings of empathy or interpersonal closeness while under the influence of MDMA [8, 15, 133, 134].

6.3. Toxicology

6.3.1. Neurotoxicity in Animals

Repeated high doses of MDMA in animals reduce total serotonin levels in the brain, impair transport of serotonin, and cause psychobehavioral changes such as increased anxiety [76, 126, 135-137]. Studies in rodents and primates suggest that MDMA could damage serotonin axons and cause neurotoxicity [76, 138-141]. However, the majority of these studies employed large doses of MDMA that overestimated human-equivalent doses, an issue that remains true even in recent investigations [see for example50, 142, 143]. It now appears that lower doses of MDMA do not reduce brain serotonin [84, 85]. Monkeys allowed to self-administer MDMA for an 18-month period had no reductions in brain dopamine, slight reductions in brain serotonin, and no chemical markers of neuronal injury [144]. Rats receiving lower doses of MDMA also fail to exhibit signs of neurotoxicity [85]. A recent report detected increases in one marker of neuronal injury without detecting any decreases in brain serotonin after administering two human-equivalent doses of MDMA to rhesus monkeys for two days [145]. Relying on previous *in vitro* and *in vivo* research and on their own current work, the same researchers present a case that MDMA is altering regulation of brain serotonin without producing damage to serotonin axons. They reach this conclusion through comparing findings of reduced brain serotonin and SERT with failure to detect other indicators of neuronal injury and findings of decreased expression of the SERT gene in rat brain [50].

6.3.2. LD50 in Animals

Intravenous MDMA doses that cause lethality in 50% of the cases, known as the LD50, are 97 mg/kg in mice, 49 mg/kg in rats, 14 to 18 mg/kg in dogs, and 22 mg/kg in monkeys [82]. The LD50 in mice housed together is 20 mg/kg, considerably lower than values in isolated animals [113, 146]. MDMA lethality also varies between the sexes and different strains in rats.[147-149].

6.3.3. Developmental Toxicity in Animals

15 mg/kg MDMA administered s.c. to pregnant rats was detected in amniotic fluid [150]. Several teams of researchers have performed studies of developmental toxicity in rodents. None of the studies found gross structural abnormalities in rats exposed to high doses of MDMA *in utero.* In an initial study, pregnant rats were administered twice-daily injections of high doses of MDMA (15 mg/kg) or saline from embryonic days (E) 14-20. Rat pups that had received MDMA showed reductions in the dopamine metabolite homovanillic acid, along with reductions in the serotonin (5-HT) metabolite 5-HIAA. Prenatally exposed MDMA animals also had reduced dopamine and serotonin turnover in the nucleus accumbens [151]. The same team reported postnatal exposure to MDMA correlated with reductions in serotonin and its metabolite, as well as significant increases in dopamine turnover and the prevalence of a dopamine metabolite in multiple forebrain structures and the brainstem. Brain-derived neurotrophic factor (BDNF), which controls neuronal growth in the brain, was significantly increased (19-38%) in all forebrain structures and in the brainstem in MDMA-exposed neonates [152]. The researchers proposed that BDNF was compensating to minimize MDMA effects. However, later studies found that neonatal MDMA exposure did not affect hippocampal concentrations of serotonin or dopamine [153] and that a region-specific enhancement in BDNF expression did not mediate the abnormal

serotonergic signaling observed following neonatal MDMA exposure [154]. Postnatal days 11 and 20 were proposed to be equivalent to the third trimester of gestation in humans [152], so it is possible that exposure to high doses of MDMA *in utero* could have developmental effects, but these do not appear to be related to BDNF levels.

Prenatal MDMA exposure at high doses significantly increased locomotor activity of pups in a 20-min novel cage environment [151]. Rodents treated with MDMA during development were not significantly different than rodents who received MDMA as adults. The results of several behavioral tests did indicate that developmental MDMA exposure combined with adult exposure may interfere with some aspects of learning [153]. Neonatal MDMA administration did not alter working memory in the object-recognition test in young adulthood (PD 68-73) and there were no differences in binding of the radiolabeled SSRI citalopram to the serotonin transporter at this age. However, the pretreated animals showed increased thermal dysregulation and serotonin syndrome responses following MDMA challenge, especially with respect to head-weaving stereotypy [155]. Another team also found that neonatal rat MDMA exposure exacerbated hyperthermic response to a subsequent dose to MDMA [156]. A study in neonatal rats suggests two distinct critical periods wherein repeated doses affected learning versus acoustic startle [157].Given differences between human and rodent development and thermoregulation, it is not clear whether such findings can be generalized to humans (see Section 6.2.4). Because there may be a critical period during which exposure to MDMA could alter development, and as a result of the relative lack of information concerning its developmental toxicity, women who are pregnant or who are not using an effective means of birth control should not receive MDMA.

6.3.4. Self-Administration in Animals

Mice, rats, and monkeys will self-administer MDMA, indicating that MDMA has rewarding properties in animals [158-160]. Monkeys choose to self-administer MDMA in doses equivalent to or only slightly higher than doses used by humans [158], but they reduced their MDMA intake over time. While monkeys will work hard to obtain MDMA, they will work harder to obtain other psychostimulants, such as cocaine or methamphetamine [161, 162]. Taken together, these results suggest that the abuse liability of MDMA is moderate.

7. Effects in Humans

Evidence exists for intentional human use of MDMA as early as the late 1960s [26], and there are records of a police seizure of MDMA in the early 1970s [163]. Shulgin and Nichols were the first to report on the effects of MDMA in humans [28]. In the 1970s, psychotherapists used MDMA-assisted psychotherapy to treat psychological disorders, including anxiety [30]. Legal therapeutic use continued until its placement in US Schedule 1 in 1985 [29, 33, 164]. Estimates indicate that 500,000 doses of MDMA were administered during psychotherapy sessions in North America prior to its scheduling [26, 164]. A few uncontrolled human studies of MDMA occurred in the 1980s [9, 165], including Greer and Tolbert's study of MDMA in a psychotherapeutic context. Recreational use of MDMA, known as "ecstasy," has been ongoing since the early 1970s, but controlled human studies of MDMA did not commence until the early to mid-1990s, with the publication of a Phase 1 dose-response safety study supported by the Sponsor and conducted by Grob and colleagues [13]. The Sponsor has completed two

investigations of MDMA-assisted psychotherapy for PTSD, one in the U.S. and one in Switzerland [21, 166, 167] with additional phase 2 studies underway.

7.1. Pharmacology and Product Metabolism in Humans

7.1.1. Pharmacology in Humans

Estimates from animal data suggest the LD50 in humans is probably between 10 - 20 mg/kg [1]. Typically, human trials have used doses between 1 and 2 mg/kg, with therapeutic studies using fixed dosing rather than adjusting dosing on a mg/kg basis, in order to achieve a more consistent subjective response between subjects. The pharmacokinetics of MDMA in humans have been characterized in blood and urine samples using oral doses of up to 150 mg MDMA.

Many researchers categorize MDMA as belonging to a unique class of drugs referred to as the entactogens [8, 31], defined as substances that produce changes in mood and social interaction, as well as feelings of interpersonal closeness and changes in perception. MDMA shares some of the pharmacological effects of stimulants and serotonergic hallucinogens [3, 6, 7, 168], as well as a small number of pharmacologically related compounds, such as methylenedioxyethylamphetamine (MDE) [168]. Retrospective reports and surveys have assessed the social cognitive effects of MDMA or ecstasy [15, 133, 134, 169]. Initial studies measured self-reported empathy or closeness to others in healthy volunteers [2, 5, 55], and recent controlled studies measured effects of MDMA on social cognition or emotion [53, 54, 56]. Although researchers have offered several models and explanations for the effects of entactogens, it appears that serotonin release plays a significant role in producing at least some of these effects, and norepinephrine release may play a lesser role. Indirect action on $5HT_{1A}$ or $5HT_{2A}$ receptors and neuroendocrine responses such as increases in the hormones oxytocin, vasopressin, prolactin, and cortisol may also play a role in producing the unique effects of MDMA.

Preventing serotonin release through administration of selective serotonin reuptake inhibitors (SSRIs) appears to attenuate or eliminate most subjective, physiological and immunological effects of MDMA [170-174]. Pre-treatment or co-administration with SSRIs attenuates the effects of MDMA on mood and perception without influencing specific effects such as nervousness or excitability [170]. Some researchers report that SSRIs attenuate MDMA-induced increases in heart rate and blood pressure [171, 174] while others report that SSRIs only attenuate elevated heart rate [173]. All three studies of SSRI pre-treatment suggest that co-administration of SSRIs with MDMA is safe, but that this combination prevents or significantly reduces the subjective effects of MDMA. These subjective effects are predominately mediated by direct or indirect action on $5HT_{2A}$ receptors [57, 132, 175], with at least one study concluding that the effects of MDMA upon positive mood are at least due in part to 5HT2A receptor activation [57]. In contrast, the $5HT_{1A}$ receptor appears to be minimally involved in producing the subjective effects of MDMA[57, 130-132]. Co-administration of the beta-blocker and $5HT_{1A}$ antagonist pindolol along with 1.5 mg/kg MDMA to 15 men attenuated self-reported "dreaminess" and pleasantly experienced derealization after MDMA without actually attenuating MDMA-related reduction in performance on a task requiring visual attention, and coadministration of pindolol to 9 men and 8 women failed to alter the acute effects of 75 mg MDMA on self-reported mood [57, 130].

Recent human MDMA studies suggest that norepinephrine (NE) release may also contribute to the pharmacodynamic, physiological and psychological effects of MDMA [176-179]. Studies with NE uptake inhibitor reboxetine suggests that norepinephrine plays a role in the cardiovascular effects of MDMA and on subjective effects on positive mood and excitement [177]. Most of the psychostimulant-like and psychological effects of MDMA are blocked after administration of the dual SSSR/NRI duloxetine [178, 179], and there is evidence that norepinephrine and serotonin may play a role in elevated copeptin, a neuroendocrine hormone, in women after MDMA [179]. Preclinical and *in vitro* findings reports indicate that MDMA displays a higher affinity for the norepinephrine transporter than the serotonin transporter [73], which could possibly explain these results (Hysek/2012).

At least some MDMA effects on mood and anxiety may result from dopamine release indirectly activating D_2 receptors, as administering the D_2 antagonist haloperidol diminished positive mood and increased anxiety in humans [180]. As of November, 2012, there have been no studies in healthy volunteers examining the role of dopamine release or uptake inhibition.

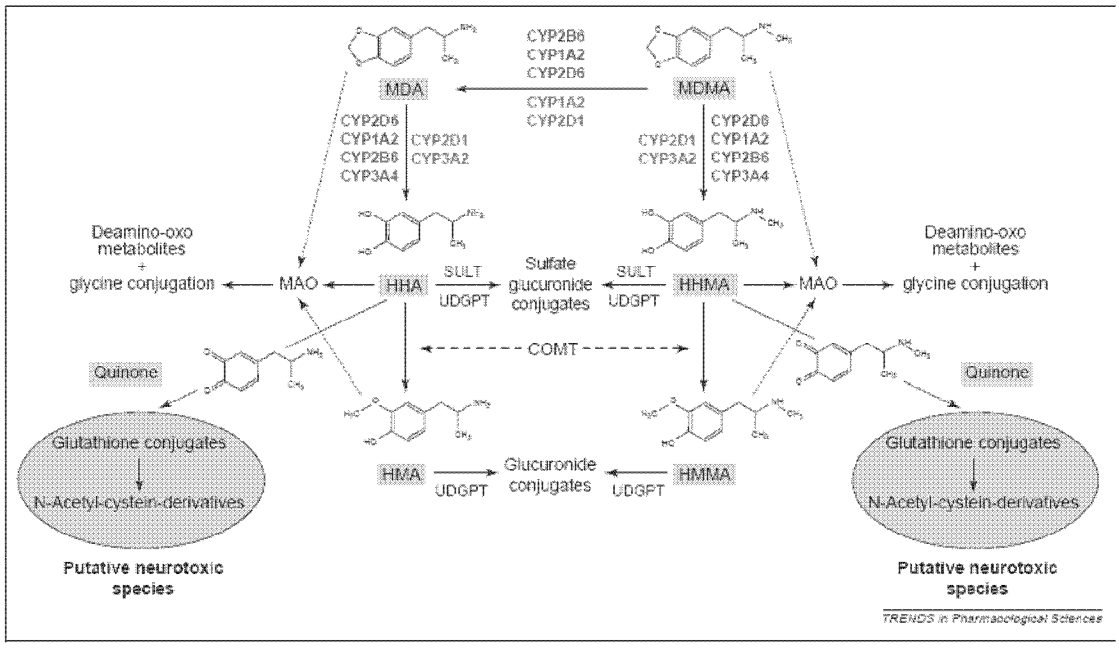


Figure 1. Metabolism of MDMA in humans (in red) compared to metabolism in rats (in blue). Reproduced with permission of R. de la Torre [181].

7.1.2. Metabolism in Humans

Metabolites of MDMA are summarized in Figure 1 [182-186]. Metabolites are primarily excreted as glucuronide and sulfate conjugates [183]. Studies examining metabolism of 100 mg MDMA reported excretion values similar to those reported by de la Torre and associates [187-191]. Urinary excretion of the MDMA metabolite HHMA after 100 mg MDMA in four men was 91.8 ± 23.8 mol and 17.7% recovery [191]. By contrast, urinary recovery of the major metabolite HMMA after 100 mg was 40% [192]. As was the case for maximal plasma values, urinary

recoveries for MDMA and MDA were higher after a second dose of 100 mg MDMA than after an initial dose of 100 mg MDMA [187]. In one study, urinary excretion of the metabolite HMMA exceeded that of MDMA by 33 hours after a dose of 1.6 mg/kg MDMA [193], suggesting that secondary metabolism of MDMA continues during this period. A study comparing the effects of a single 100 mg dose with an initial administration of 50 mg followed 2 hours later by 100 mg reported higher peak plasma MDMA than might be expected, and lower levels of the MDMA metabolites HMMA and HMA [194]. Findings support the enantioselective metabolism of MDMA and its metabolites measured in blood and urine [195, 196].

Onset of MDMA effects occurs 30 to 60 minutes after administration [3, 4], peak effects appear 75 to 120 minutes post-drug [2, 5-7], and duration of effects lasts from three to six hours [5, 6, 8], with most effects returning to baseline or near-baseline levels six hours after drug administration. Self-reported duration of effects may increase with as the dose of MDMA increases [2]. Orally administered MDMA has a half-life of seven to nine hours in humans, with one report listing a half-life of 11 hours [188]). It is metabolized in the liver by several cytochrome P450 CYP enzymes, including CYP1A2, CYP3A4, and CYP2D6. It is likely that active doses of MDMA inhibit CYP2D6 function as measured by examining the effects of MDMA on dextromethorphan metabolism. Because O'Mathuna and colleagues present evidence that CYP2D6 activity may not fully recover until ten days after MDMA [197, 198]. After reviewing their data and the literature on MDMA pharmacokinetics, de la Torre and colleagues concluded variation in CYP2D6 genotype is not clinically significant, due in part to the fact that the enzyme is inhibited in most people after administration of an active dose [199]. In contrast, MDMA may produce increased activity of the enzyme CYP1A2, as evidenced by comparing caffeine metabolism before and after MDMA [200]. The enzyme COMT and monoamine oxidase may also be involved in the metabolism of MDMA [192]. At least one variation in COMT genotype may affect MDMA elimination rate (Ke) and systolic blood pressure (SBP) after MDMA [201].

7.2. Physiological Effects in Humans

7.2.1. Endocrine Effects in Humans

MDMA acutely increases cortisol, prolactin, and adrenocorticotropic hormone concentrations in a dose dependent manner [4, 5, 13, 56, 187, 202], whereas growth hormone is unchanged by up to 125 mg MDMA [4]. Increases in cortisol and prolactin peak at about 2 hours after MDMA administration [4, 13]. A second dose of 100 mg MDMA, given four hours after an initial 100 mg, produces a second increase in cortisol during an interval when cortisol levels are declining [203], and a dose of 100 mg MDMA, given 24 hours after an initial dose, stimulates a greater release of cortisol but not prolactin [187]. A naturalistic study in clubgoers found a much greater elevation in cortisol after ecstasy use [204]. In a study of the effects of 0.5 and 1.5 mg/kg MDMA in eight people, there was a trend for increased levels of the hormone dehydroepiandrosterone (DHEA) after 0.5 mg/kg MDMA, and a significant increase after 1.5 mg/kg MDMA, with peak levels appearing 2 to 3 hours post-drug [5]. MDMA produces a robust increase in the neurohormone oxytocin [54], a finding first seen in a naturalistic study [205]. The naturalistic study reported elevated levels of the hormone oxytocin in clubgoers with detectable blood MDMA levels when compared to clubgoers without any detectable levels of MDMA. It is likely that all neuroendocrine changes result from monoamine release, and it is currently

unknown what role, if any, they play in producing the effects of MDMA. Exogenous oxytocin increases trust and improves accuracy of emotion perception, and increased cortisol, in some circumstances, may serve as a signal to seek affiliation or to increase positive mood [206-209].

The significance of elevated oxytocin in producing changes in social cognition are discussed in section 7.1, and include potentially therapeutic effects, such as increased feelings of closeness to others or greater ability to detect expressions of positive mood in others. The significance of elevated cortisol after MDMA is unclear. It is possible that cortisol elevation could be tied to specific acute effects on mood or memory. However, pre-treatment with the cortisol synthesis inhibitor Metyrapone blocked MDMA-induced increase in cortisol levels in blood without preventing impaired performance on verbal memory tasks and without altering the effects of MDMA on mood, [210]. It is unclear what contributions, if any, elevated cortisol make to the subjective or physiological effects of MDMA.

7.2.1.1. Endocrine Effects and Homeostasis in ecstasy users

A number of case reports describe hyponatremia after uncontrolled, non-medical ecstasy use [83, 211-213]. Behavioral factors, including vigorous exercise and excessive consumption of water without an attempt to replace electrolytes, and an increase in the anti-diuretic hormones arginine vasopressin and oxytocin, likely all contribute to this very rare but serious adverse event in ecstasy users [205]. Hyponatremia has not occurred during a controlled clinical trial with MDMA.

7.2.2. Thermoregulatory Effects in Humans

In the first Phase 1 safety study funded by the Sponsor, MDMA was found to cause a significant increase in body temperature and heart rate in some healthy volunteers [13]. However, these increases were found to be transient and tolerable in a controlled clinical setting. Doses between 1.5 and 2 mg/kg MDMA produced only a slight elevation in body temperature that was not clinically significant [6, 171, 175] and this elevation was unaffected by ambient temperature [117]. Studies in MDMA-experienced volunteers given 2 mg/kg MDMA produced slight but statistically significant increases in core body temperature, at mean elevation of 0.6 ° C [117]. The same study found that ambient temperatures did not affect elevation in core temperature after administration of MDMA, which increased metabolic rate. A second dose of MDMA elevates body temperature, but not beyond what would be expected after the cumulative dose [194].While MDMA did not increase or decrease perspiration overall, it was associated with a higher core temperature when people began perspiring. Ambient temperature neither attenuated nor amplified the subjective effects of MDMA, with people reporting similar drug effects in the warm and the cool environment. As expected, people felt warm when the room was warm and cold when the ambient temperature was cool, and MDMA did not distort perceptions of warmth or cold in either case. Unlike rodents given MDMA at higher mg/kg doses, humans do not exhibit reduced temperature when MDMA is given in a cold environment, and they do not exhibit significant hyperthermia in a warm environment. When compared with placebo, findings from 74 participants given MDMA found that men exhibited a greater elevation in body temperature than women when given the dose of MDMA in milligrams per kilogram [6]. Subsequent studies have not confirmed this gender difference [11], and a report in a sample of 17

men and women reported higher oral temperatures in women [201]. It is notable that participants in studies in a clinical setting have not engaged in vigorous exercise and have remained either sitting or lying down throughout most drug effects. It may be the case that ambient temperature and vigorous exercise contribute to the occurrence of hyperthermia in people ingesting ecstasy in uncontrolled settings. However, one out of two naturalistic studies reported that ecstasy users had a slight but not statistically significant increase in body temperature, while two others failed to find any significant differences in ecstasy-user body temperature at a club [204, 214, 215].

Hyperthermia has occurred in people using ecstasy in unsupervised and non-medical conditions, and though rare, it is one of the most frequently reported serious adverse events occurring in ecstasy users [212, 216]. The exact conditions preceding hyperthermia are unknown. Even if ambient temperature does less to moderate the effects of MDMA on body temperature than originally believed, other environmental and behavioral factors, as those related to vigorous exercise, may be involved. At least one case series of individuals seen on the same night and near or in the same nightclub suggest a relationship between ecstasy dose and likelihood of hyperthermia [217]. A case report and some findings in rodents suggest that hyperthyroidism or thyroid dysregulation may play a role in MDMA-related hyperthermia in humans [218, 219]. No cases of hyperthermia have been reported in clinical trials with MDMA.

7.2.3. Cardiovascular Effects in Humans

MDMA produces sympathomimetic effects that include elevation in blood pressure and heart rate, first recorded by Downing [9] and replicated by other research teams in the US and Europe [4, 6, 10]. Subsequent trials confirmed that MDMA produced significant increases in heart rate and blood pressure that were likely to be well tolerated by healthy individuals [2, 5, 11, 12]. Most people do not experience elevations that are greater than those seen after moderate exercise. Cardiovascular effects of MDMA first appear 30 to 45 minutes after administration [9] and peak between 1 and 2 hours post-drug [7, 10], with effects waning 3 to 5 hours after drug administration. Men given the same mg/kg dose of MDMA as women exhibited a significantly greater elevation in blood pressure and greater elevation in heart rate in a study summarizing and pooling data from a series of human MDMA studies [6]. These studies did not report any discomfort or increased distress accompanying cardiovascular effects.

Elevation in blood pressure above 140/110 or higher occurred in approximately 5% of research participants receiving a single dose of at least 100 mg MDMA in research studies [4, 8]. Peiro and colleagues observed elevation in blood pressure above 150/90 as well in all ten participants given 50 mg followed two hours later by 100 mg MDMA [194]. None of these individuals needed clinical intervention and blood pressure returned to normal as drug effects waned [4, 8, 194].

The alpha(1) – and beta-adrenergic receptor antagonist carvedilol reduced MDMA-induced elevations in blood pressure, heart rate, and body temperature when administered 1 h before MDMA without affecting the subjective effects of MDMA. Hence carvedilol could be useful in the treatment of cardiovascular and hyperthermic complications associated with ecstasy use [220].Other antihypertensive medications either alter some of the effects of MDMA [221] or do not significantly reduce blood pressure [176].

As described above, administering 50 mg MDMA followed two hours later by 100 mg produces elevated HR and BP, but the elevations are no greater than those expected with plasma MDMA levels [194]. The study used a different dosing regimen than the one used in sponsor-supported studies.

The elevation of blood pressure and increased heart rate produced by MDMA, like that produced by other sympathomimetic drugs, can lead to additional risks and complications [222-224], such as stroke, cardiac events, or other cerebrovascular events, including cerebral venous sinus thrombosis [225] and cerebral or subarachnoid hemorrhage [41, 226-229]. In two such cases, a previously existing underlying arteriovenous malformation appeared to play a role in the event [226, 228]. Increased heart rate (tachycardia) and elevated blood pressure can also lead to cardiac events, such as arrhythmias or myocardial infarction [230, 231]. Although the presence of MDMA was rarely confirmed in reported cases, these types of events are all well established complications of hypertension and can occur after use of amphetamines. There have been no such events to date in any clinical trial of MDMA.

Some researchers expressed concern that MDMA activity at $5HT_{2B}$ receptors might be indicative of increasing risk of valvular heart disease with repeated use [69]. Studies in ecstasy users indicated that only people reporting average lifetime exposure of 900 tablets had cardiac abnormalities indicative of potential valvular heart disease [232], and a case of valvular heart disease has occurred in a man reporting approximately 16 years of ecstasy use [233]. No abnormalities were found in people reporting lifetime exposure of approximately 200 tablets in the same study. Previous to this, ECGs in eight ecstasy users also failed to find any cardiac abnormalities [10]. Since VHD-associated changes and VHD only occurred after extremely heavy ecstasy use, they are unlikely to be a risk within the research or therapeutic context.

7.2.4. Liver Effects in Humans

Hepatotoxicity (liver disease or damage) was reported in approximately 16% of 199 case reports from non-medical, uncontrolled ecstasy users collected from the mid-1990s to 2001, making it the third most common serious adverse event in reported in the literature [83]. There appears to be more than one pattern of ecstasy-related hepatotoxicity, and a number of factors, including polydrug use and setting of use may be involved [234]. Acute liver failure or hepatitis has occurred after reported ingestion of a single ecstasy tablet [235-237]. In other cases, hepatotoxicity has occurred after months of regular ecstasy use [238]. Standard toxicity studies failed to find liver damage after MDMA in rats or dogs after 28 days of exposure [239], nor have any cases of liver disease arisen during controlled studies. Examinations of case reports and a number of *in vitro* studies suggests an association between hyperthermia and hepatotoxicity. However, liver disease also occurred in some individuals without the occurrence of hyperthermia, with it appearing after continued use and resolving after abstinence. In these cases, it appeared after continued use and resolved after a period of abstinence. These reports suggest a potential immunological response. Because hepatotoxicity has been noted in ecstasy users, *in vitro* and *in vivo* studies have examined the hepatotoxicity of MDMA. These studies show that high doses of MDMA can impair liver cell viability [240], increase profibrogenic activity in cultured stellate cells [241], and slightly reduce cell viability without producing lipid peroxidation [242]. However, peak liver exposure to MDMA in Sponsor studies should be

approximately one-eleventh the concentration shown to impair cell viability in these *in vitro* studies. No cases of liver disease or hepatotoxicity have occurred in a controlled clinical trial with MDMA.

7.2.5. Immunological Effects in Humans

Studies in men conducted by researchers in Spain have found 100 mg MDMA to have immunosuppressive and anti-inflammatory effects [172, 203, 243, 244]. Findings included a decline in CD4 cells, smaller CD4/CD8 ratio, attenuated lymphocyte proliferation in response to mitogen, and an increase in natural killer (NK) cells, with effects diminishing but still detectable 24 hours after drug administration. These researchers also found that MDMA decreased production of pro-inflammatory cytokines, including IL-2 and interferon-Gamma, and increased production of anti-inflammatory cytokines, including IL-4 and IL-10. Generally, MDMA appeared to decrease the concentration of Th1 (immunostimulating and pro-inflammatory) cytokines and increase the amount of Th2 (immunosuppressive and anti-inflammatory) cytokines measured in blood. Changes of similar magnitude and duration have been previously noted after ingestion of other psychoactive agents, such as alcohol or cocaine [244, 245]. Because of their limited duration, these changes are not likely to have clinical significance beyond several days of possible increased risk of viral upper respiratory infection or similar illness. Immunological changes seen after an initial dose of MDMA are enhanced by a second dose of identical size given four hours after the first dose [203, 246]. A second dose of identical size given 24 hours after the first dose produced the same immunological effects over the same time course, but with greater intensity than after the first dose [203]. Given this data, it is possible that administering a smaller supplemental dose 1.5 to 2.5 hours after the first dose will slightly enhance the immunological effects set in motion by the first dose. Previous Phase 1 studies have not reported any indication of increased risk of illness occurring after MDMA administration.

7.2.5.1. Immunological Effects in Ecstasy Users

A longitudinal study of regular ecstasy and cannabis users found a sustained reduction in interleukin 2 (IL-2), increased levels of transforming growth factor-Beta (TGF-B) and reduced CD4 cells, and regular ecstasy and cannabis users reported experiencing a greater number of mild infections than occasional ecstasy and cannabis users on a structured questionnaire [247].

7.2.6. Effects on Sleep in Humans

Serotonin and catecholamine neurotransmitters are known to modulate sleep architecture and alertness. To date, there is only a single study examining the acute effects of MDMA on sleep [248] while all other investigations have looked at sleep in ecstasy users. In a trial with 2 mg/kg MDMA given six hours prior to preparing for sleep, MDMA was found to increase Stage 1 sleep and reduce rapid eye movement (REM) sleep without producing an increase in daytime sleepiness [248].

7.2.6.1. Effects on sleep in ecstasy users

Examining sleep architecture in ecstasy users, the same investigators found less total sleep time and less stage 3 and 4 sleep on the adaptation night, but no overall differences in sleep architecture [248]. Another study comparing heavy ecstasy users with non-drug using controls

found no differences in baseline sleep using electroencephalography (EEG) [249]. Early studies in mostly heavy ecstasy users reported significant decreases in total sleep as well as stage 2 sleep [250], while recent studies found ecstasy users were able to fall asleep more easily upon depletion of catecholamine neurotransmitters suggesting an underlying difference in serotonergic control of sleep architecture[251, 252]. Findings of sleep disruption in ecstasy users are not likely applicable to the exposures seen in research or therapeutic settings.

A study of breathing during sleep in 71 ecstasy users and 62 polydrug users did not find overall differences in disrupted breathing, assessed via nasal cannula, but found that all moderate and severe breathing disruptions occurred in the ecstasy using sample [253]. McCann and colleagues reported a relationship between cumulative (lifetime) ecstasy exposures and instances of disrupted breathing during non-REM sleep and suggested ecstasy users could be vulnerable to potentially fatal sleep apnea. In contrast, other researchers failed to find greater night-time awakenings indicative of sleep apnea in ecstasy users [248, 249], and the high rate of disrupted breathing McCAnn and colleagues detected even in the controls suggest that this measure may not provide clinically significant assessments. Taken together, it appears that MDMA acutely produces lighter sleep with fewer REM periods.

7.3. Reproductive and Developmental Risks in Humans

Previous research supported a possible link between ecstasy use and birth defects [254], while an epidemiological study of a large cohort of pregnant women in England conducted in 2004 failed to support this link, at least in respect to a specific cardiac defect [255]. However, the authors also stated that exposure to MDMA in their sample was too low to establish risk. An earlier survey of a drug-using population suggests that most women cease using ecstasy when they learn they are pregnant [256]. A 2012 survey of 96 women in the UK interviewed about their drug use during pregnancy found a link between self-reported extent of prenatal MDMA exposure and delays in infant development at 12 months, with heavily exposed infants delayed in mental and motor development but not language or emotional development [257].

There are no plans to include pregnant women in research studies with MDMA.

7.4. Abuse Potential in Humans

Studies in humans and animals suggest MDMA possesses some abuse potential. Of the small number of individuals assessed in a representative sample of Munich residents aged 14 to 24, only 1% were diagnosed with ecstasy abuse and 0.6% with dependence [258], though other reports of non-representative samples have reported higher percentages of MDMA abuse or dependence [259], and approximately 25% of polydrug users who had used ecstasy reported abuse or dependency [260]. When reviewing the effects of MDMA in a sample of 74 largely drug-naïve participants, Liechti and colleagues stated that "none of the participants expressed any interest in taking MDMA as a recreational drug" after receiving MDMA in a controlled research setting [6]. Only one of 32 participants enrolled in sponsor-supported studies of MDMA-assisted psychotherapy for PTSD reported taking ecstasy outside the confines of the study and failed to reproduce the experience [166]. Several participants volunteered that they would not seek out ecstasy outside of therapy. All 12 participants enrolled in the study of MDMA-assisted psychotherapy in Switzerland did not test positive for stimulants or MDMA

[167]. It also appears that MDMA has fewer or less intensely rewarding effects than stimulants, and even heavy ecstasy users fail to report the intensive patterns of use seen with other stimulants. Hence MDMA possesses moderate abuse liability that is greater than that for serotonergic hallucinogens but less than that for stimulants.

7.5. Neuropsychological Effects in Humans

7.5.1. Subjective Effects in Humans

MDMA alters mood, perception, and cognition. At doses of at least 1 mg/kg (or approximately 70 mg) and higher, active doses of MDMA alter mood and cognition and produce slight alterations in perception [6, 261]. Effects peak 90 to 120 minutes after oral administration and they are near to or at pre-drug levels three to six hours later [8, 262, 263]. Sub-acute effects may occur one to three days after drug administration, but are no longer apparent seven to 14 days later [5, 264, 265]. Most of the therapeutic effects of MDMA result from changes in affect, cognition, and social interaction. When combined with psychotherapy that supports one or more of these effects, MDMA permits people to confront and consider emotionally intense memories, thoughts, or feelings, and perhaps through changes in mood and perception, increases empathy and compassion for others and the self [24, 165, 266]. Though a naturalistic study reported that ecstasy increased accuracy of assessing at least some emotional expressions [267], a controlled study with 0.75 and 1.5 mg/kg MDMA failed to replicate this finding [11].

7.5.2. Emotional Effects in Humans

MDMA increases positive mood and anxiety [3, 5-7]. MDMA users report feeling more talkative and friendly after receiving MDMA, Self-reported interpersonal closeness was noted during a study in healthy volunteers [8]. Subsequent research confirmed the occurrence of increases in interpersonal closeness after MDMA [53-56, 173]. Researchers using two items within an instrument designed to assess drug effects and a visual analog scale rating closeness to others failed to detect increased feelings of empathy after 1.5 mg/kg MDMA [5], possibly due to the low sensitivity of this measure. However, a recent investigation into the effects of pretreatment with the SSRI paroxetine on MDMA effects in humans reported that MDMA increased feelings of being social and closeness to others, and that paroxetine reduced these effects [174]. People reported feeling anxious and undergoing negatively experienced derealization, including increased anxiety related to loss of control and experiences of racing or blocked thoughts [3, 6, 8].

People receiving active doses of MDMA experienced euphoria, positive mood, vigor, and positively experienced derealization, consonant with early retrospective reports, and they also experienced anxiety, tension, and dysphoria, as concern over losing control over the self [3, 5-7]. More surprisingly, participants report increased positive mood even after a dose of 25 mg [268]. It is uncertain whether the increases in positive and negative mood occur simultaneously or occur at different times throughout the duration of MDMA effects; there is some suggestion in reports from two different teams that peaks in negative mood may precede peaks for positive mood [7, 180]. MDMA may have a greater impact on mood in women than in men. Women report greater elevation in negative mood. A second dose of MDMA does not increase subjective effects beyond effects reported after an initial dose, results which Peiro and colleagues interpreted as

indications of tolerance to these effects [194]. It is notable that the second dose in this study was double that of the first dose, in contrast to sponsor-supported studies, wherein the second dose is half the size of the initial dose.

Positron emission tomography (PET) brain scans 75 minutes after administration of 1.7 mg/kg MDMA found increased regional cerebral blood flow (rCBF) in ventromedial prefrontal, inferior temporal, and cerebellar areas and decreased rCBF in the left amygdala [269]. Decreased activity in the amygdala may be indicative of reduced reactions to potential threats [270]. An fMRI study conducted by Bedi and colleagues found that 1.5 and 0.75 mg/kg MDMA reduced signaling in the amygdala in response to angry faces when compared with placebo, though without changing the response to faces showing fear [11]. These researchers also detected increased activity in the ventral striatum in response to happy faces. Taken together, these findings suggest that MDMA changes the way emotional facial expressions are processed or the response to them. Complimenting these findings are results from Hysek and colleagues demonstrating that MDMA enhanced the accuracy of recognizing faces exhibition expressions of positive mood, impaired mind reading for facial expressions of negative mood, and had no effect on mind reading for neutral stimuli [56]. Hysek suggests that the enhanced mind reading of positive emotions may facilitate therapeutic relationships in MDMA-assisted psychotherapeutic settings. There is also some evidence for MDMA producing selective difficulty in recognizing faces expressing fear Baggott, 2008 #1606}.

7.5.2.1. Emotional effects in ecstasy users

Retrospective surveys of people who have used MDMA or ecstasy offer similar accounts of MDMA effects to those reported in controlled studies. These studies surveyed or interviewed members of several populations, including college students, psychotherapists, and individuals recruited via word of mouth or in public spaces. Study respondents report experiencing stimulant-like effects, such as greater energy or talkativeness, and hallucinogen-like effects, including as perceptual changes or poor concentration. They also report that ecstasy increased feelings of closeness, compassion, or empathy toward the self or others [15, 133, 134, 271]. The disparity in detection of entactogenic effects in retrospective versus controlled studies is largely due to failure to measure these effects, but might also relate to aspects of setting in controlled studies that do not permit enough unstructured interpersonal contact to produce or facilitate feelings of interpersonal closeness.

Psychiatric problems after uncontrolled, non-medical ecstasy use were reported in 22.1% of 199 case reports from the early 1990s to 2001, and are the most common reason for appearance at an emergency department [83]. Psychiatric symptoms included affective responses, such as dysphoria, anxiety, panic, and psychotic response, as well as cases with mixed psychotic and affective features. The most common problem reported as psychotic response, as seen in [272]. The mechanisms behind ecstasy-associated psychiatric problems remain unclear but are likely the result of an interaction between pharmacology and individual susceptibility. The difficulty of assessing the frequency of these events is increased given that that pre-existing psychiatric problems occur in people who choose to use ecstasy [273] and findings of an association between use of ecstasy and other drugs and self-reported symptoms of anxiety and depression. As described earlier, most cases of psychological distress after ecstasy use resolved after supportive care [216, 274]. Anxiety responses associated with MDMA administration reported in

controlled trials have resolved over time, usually either during the period of acute drug effect or with the waning of drug effects.

Previous reports have found an association between ecstasy use and increases in symptoms of depression or anxiety, (see for example [275, 276]). A meta-analysis of self-reported depressive symptoms detected an association between ecstasy use and scores on the Beck Depression Inventory (BDI), a popular self-report measure of depression symptoms [277]. However, the association was strongest in studies with small samples, and drug use variables were often incompletely reported and not verified through any methods save self-report in the studies analyzed. Many studies found that increases in self-reported anxiety or depression were more strongly related to polydrug use rather than to use of any one substance [278-281]. One found an equal or stronger association between regular use of cannabis, and not ecstasy, and anxiety, depression or other psychological problems [282].

7.5.3. Effects on Perception in Humans

Study participants receiving MDMA experienced slight changes in visual or auditory perception, including changes in the brightness of the room or colors, sounds seeming closer or farther away, and simple visual distortions [2, 3, 5, 6]. Participants also experienced altered time perception and changed meaning or significance of perceptions after MDMA [8]. People maintained insight as to their experience, and there was little indication that MDMA produced any strong alterations to the sense of self or control over the experience [5, 7]. Healthy volunteers reporting unusual beliefs retained a degree of insight [5]. Women reported experiencing all subjective effects of MDMA more intensely, but especially those related to perceptual changes [6]. The perceptual effects of MDMA appear to be the result of direct or indirect action on $5HT_{2A}$ receptors, as coadministration of the $5HT_{2A}$ antagonist ketanserin reduced reported perceptual alterations as well as eliminating slight elevations in body temperature after 1.5 mg/kg MDMA [175], while co-administration with the 5HT1A antagonist pindolol did not [130].

7.5.4. Cognitive Effects in Humans

MDMA does not affect responses on tasks requiring attention and response to visual stimuli or visually presented words [8, 269], but interferes with performance on digit-symbol substitution, a measure of attention, psychomotor speed and visual memory [3]. A dose of 75 mg improved visual tracking speed but impaired estimating the position of a blocked (occluded) object in a study of acute effects on skills used in driving cars [262]. A recent series of studies conducted in the Netherlands that examined the effects of MDMA on skills needed for automobile driving reported transient and selective changes in verbal and visual attention and memory after 75 or 100 mg MDMA [283-286]. MDMA caused difficulty learning or remembering lists of words and difficulty recalling object position within an array of objects. MDMA did not cause impairment in spotting scene changes and reduced weaving in a driving simulation. MDMA was associated with an excessively cautious response to the actions of another car in an assessment of actual driving [287]. MDMA acutely improved performance on one measure of impulsivity while failing to affect performance on other impulsivity measures [284]. The causes of these changes are unclear but may relate to changes in attention, salience of visual objects, and altered time perception. Changes in visuospatial recall and driving skills are likely associated with serotonin release or indirect action on serotonin receptors, as the noradrenergic and dopaminergic drug

methylphenidate (Ritalin) did not produce similar changes [283, 286, 287]. Administering a 5HT2A receptor antagonist but not a 5HT1A antagonist reduced impaired performance on a word learning and recall task after MDMA, suggesting that interference is due in part to direct or indirect activation of these receptors [132]. These changes in cognitive function and psychomotor skills occurred during peak drug effects but were not detectable 24 hours later.

In the sponsor-supported study of MDMA-assisted psychotherapy in people with PTSD, Mithoefer and colleagues did not detect significant differences in cognitive function between participants who received two doses of MDMA and participants who received placebo [21]. These findings suggest that MDMA given within a clinical trial does not produce impaired cognition.

7.5.4.1. Long-term cognitive effects in ecstasy users

Many investigations have examined cognitive function in ecstasy users. Rogers and colleagues performed a meta-analysis on a large number of retrospective studies of ecstasy users and various cognitive functions. Given methodological flaws in this type of analysis, the investigators cautiously concluded that there may be a significant effect of ecstasy use on verbal memory, and a lesser effect on visual memory [40]. Two meta-analyses of memory in ecstasy users arrived at somewhat contradictory conclusions [288, 289]. Both detected an association between ecstasy use and impaired performance on at least some measures of memory. However, one reported that this association had a medium to large effect size with no effect of ecstasy dose[288], while the other reported that the association had a small to medium effect size with an ecstasy dose effect, and that polydrug use itself contributed to impaired cognitive function [289]. A meta-analysis comparing current ecstasy users and drug-using controls on visuospatial skills reported that current users performed less well on measures of visual recall, recognition and item production than controls [290], but found no significant relationship between lifetime ecstasy use visuospatial task performance.

The only study attempting to address effects of ecstasy use on cognitive function in middle aged versus younger users and did not find a greater degree of impairment. Schilt and colleagues reported impaired verbal memory in people who began using ecstasy in their 30s compared with age-matched drug-naïve and polydrug using controls reporting some lifetime ecstasy use, but did not find a greater effect size for ecstasy use in this sample than in samples of younger ecstasy users, leading them to conclude that ecstasy use does not have a greater impact on cognitive function in older users [291].

In a prospective study comparing cognitive function in people before and up to 18 months after reported initiation of ecstasy use, Schilt and colleagues found an association between ecstasy use and performance on measures of verbal memory, but not attention or working memory [292]. All scores were within normal range; people who did not use ecstasy showed greater improvement in performance at the second time of assessment than people reporting some use. A second prospective study examined working memory in people reporting ecstasy use similar to subjects in Schilt's study with controls, and failed to find any significant differences in working memory and selective attention [293].