MAPS
MULTIDISCIPLINARY ASSOCIATION FOR PSYCHEDELIC STUDIES

Investigator's Brochure

SPONSOR	Multidisciplinary Association for Psychedelic Studies (MAPS) 1115 Mission Street Santa Cruz, CA 95060
PRODUCT	3,4-methylenedioxymethamphetamine (MDMA)
IND #	063384
DATA CUT-OFF DATE	30 April 2020
VERSION DATE	17 August 2020
EFFECTIVE DATE	31 August 2020
EDITION	12th Edition
REPLACES	11th Edition (dated 10 July 2019)

Table of Contents

List of Tables **5**
List of Appendix Tables **7**
List of Figures **9**
List of Abbreviations **10**
1.0 Summary **12**
2.0 Introduction **15**
3.0 Physical, Chemical, and Pharmaceutical Properties and Formulation **17**
4.0 Nonclinical Studies **19**
4.1 Nonclinical Pharmacology 19
4.1.1 Primary Pharmacodynamics 21
4.1.2 Secondary Pharmacodynamics 23
4.1.3 Safety Pharmacology 24
4.1.3.1 Central Nervous System 24
4.1.3.2 Cardiovascular System 29
4.1.3.3 Respiratory System 30
4.1.3.4 Hepatic System 30
4.1.3.5 Renal System 30
4.1.4 Pharmacodynamic Drug Interactions 31
4.2 Pharmacokinetics and Product Metabolism in Animals 32
4.2.1 Absorption 32
4.2.2 Distribution 33
4.2.3 Metabolism 33
4.2.4 Elimination 35
4.2.5 Pharmacokinetic Drug Interactions 35
4.3 Toxicology 36
4.3.1 Single-Dose Toxicology Studies 36
4.3.2 Repeat-Dose Toxicology Studies 37
4.3.3 Genotoxicity 38
4.3.4 Carcinogenicity 39
4.3.5 Reproductive and Developmental Toxicity 39
4.3.6 Other Toxicity Studies 41
4.3.6.1 Immunological Effects 41
4.3.6.2 Mechanistic Studies 42
4.3.6.3 Abuse Potential 44
5.0 Epidemiological and Naturalistic Evidence Summary **45**
5.1 Serious Reports of Incidents, Mortality, and Morbidity 45
5.1.1 Thermoregulatory Disorders 48
5.1.2 Cardiac Disorders 49
5.1.3 Metabolism and Nutrition Disorders 50
5.1.4 Hepatobiliary Disorders 51
5.1.5 Blood and Lymphatic System Disorders 51
5.1.6 Injuries, Poisonings, and Procedural Complications 51
5.1.7 Gastrointestinal Disorders 52
5.1.8 Respiratory, Thoracic, and Mediastinal Disorders 52
5.1.9 Psychiatric Disorders 52
5.1.10 Nervous System Disorders 53

5.2 Cognitive Function and Performance 54
6.0 Effects in Humans in Clinical Settings 56
6.1 History of Use in Clinical Settings 56
6.1.1 Phase 1 Studies 62
6.1.2 Phase 2 Studies 62
6.1.2.1 Study MP-8 63
6.1.2.2 Study MP-12 63
6.1.2.3 Study MP16 63
6.1.2.4 Other Phase 2 Studies 64
6.1.3 Phase 3 Studies 64
6.1.4 Non-PTSD Indication Phase 2 Studies 64
6.2 Pharmacology in Humans 65
6.2.1 Pharmacokinetics and Product Metabolism in Humans 65
6.2.1.1 Absorption 66
6.2.1.2 Distribution 66
6.2.1.3 Metabolism 66
6.2.1.4 Elimination 68
6.2.1.5 Pharmacogenomics 69
6.2.1.6 Pharmacokinetic Drug Interactions 70
6.2.2 Pharmacodynamics 71
6.2.2.1 Primary Pharmacodynamics 71
6.2.2.2 Secondary Pharmacodynamics 73
6.2.3 Physiological Effects 74
6.2.3.1 Central Nervous System 74
6.2.3.2 Cardiovascular System 78
6.2.3.3 Hepatic System and Other Laboratory Values 78
6.2.3.4 Renal System 79
6.2.3.5 Immune System 80
6.2.3.6 Reproductive System 80
6.2.3.7 Cognition and Performance 81
6.3 Efficacy of MDMA Across Populations 82
6.3.1 PTSD 82
6.3.2 Social Anxiety in Autistic Adults 84
6.3.3 Anxiety Associated with Life-Threatening Illness 85
6.4 Safety of MDMA in Humans 85
6.4.1 Adverse Events 87
6.4.1.1 Commonly Reported Reactions 87
6.4.1.2 Spontaneously Reported Reactions 88
6.4.1.3 Adverse Events Summary 98
6.4.1.4 Serious Adverse Reactions 109
6.4.2 Suicidal Ideation and Behavior 110
6.4.3 Vital Signs 116
6.4.3.1 Body Temperature 116
6.4.3.2 Cardiovascular System 118
6.4.4 Hepatic System and Other Laboratory Values 125
6.4.5 Cognition and Performance 126
6.4.6 Abuse Potential 128
7.0 Summary of Data and Guidance for the Investigator 137

7.1 Pharmacology 138
7.2 Toxicology 139
7.3 Physiological Effects 141
7.3.1 Adverse Events 141
7.3.2 Suicidal Ideation and Behavior 142
7.3.3 Vitals 143
7.3.4 Immunological Effects 145
7.3.5 Hepatic Effects and Other Laboratory Values 145
7.4 Risk Assessment and Mitigation 146
7.4.1 High Level Risks 146
7.4.2 Medium Level Risks 146
7.4.3 Low Level Risks 149
7.4.4 Minimal Risks 150
7.5 Reference Safety Information for Regulatory Reporting 151
8.0 Conclusions 152
Appendix 154
References 198

List of Tables

Table 1: Summary of Completed and Planned Nonclinical Toxicology Studies 20
Table 2: Pharmacokinetic Constants for Plasma MDMA After Various Routes of Administration to Humans or Animals 35
Table 3: Summary of Published Morbidity and Mortality Reports 46
Table 4: Summary of Completed Sponsor Supported Trials with MDMA 58
Table 5: Summary of Ongoing and Planned Sponsor Supported Trials with MDMA 60
Table 6: List of All Clinically Significant Changes in Laboratory Values in Two Participants from MP-2 79
Table 7: Average ALT Values at Baseline and 2-Month Follow-up After Two Experimental Sessions in Participants from MP-1 79
Table 8: Relative Incidence of Spontaneously Reported Reactions at Any Severity During Experimental Sessions in Sponsor-Supported Phase 2 PTSD Studies of MDMA-Assisted Psychotherapy MP-1, MP-2, MP-4, MP-9, MP-8, MP-12 (N=105) 90
Table 9: Relative Incidence of Spontaneously Reported Reactions During Telephone Contact on Day 1-7 After Experimental Sessions in Sponsor-Supported Phase 2 PTSD Studies of MDMA-Assisted Psychotherapy MP-1, MP-2, MP-4, MP-8, MP-9, MP-12 92
Table 10: Adverse Events by Body System Organ Class (MedDRA 17.1) At Any Severity among Participants with PTSD in Sponsor-Supported Phase 2 Studies of MDMA-Assisted Psychotherapy 99
Table 11: Severe Adverse Events by Body System Organ Class (MedDRA 17.1) among Participants with PTSD in Sponsor-Supported Phase 2 Studies of MDMA-Assisted Psychotherapy 105
Table 12: Upper Respiratory Tract Infections among Participants with PTSD in Sponsor-Supported Phase 2 Studies of MDMA-Assisted Psychotherapy 107
Table 13: Serious Adverse Reactions in Sponsor-Supported Studies of MDMA-Assisted Psychotherapy Across Indications as of April 31, 2020 109
Table 14: C-SSRS Positive and Serious Responses During Screening, Experimental Sessions Including Integrative Sessions, and Post-treatment for PTSD Studies MP-4, MP-8, MP-9, MP12, MP16, MP17 and MPVA-1* 113
Table 15: Pre-Drug, Peak, and Final Body Temperature (ºC) During Experimental Sessions with Placebo or any MDMA Dose in MAPS-Sponsored Studies of PTSD (MP-1, MP-2, MP-4, MP-8, MP-12) 116
Table 16: Pre-drug, Peak, and Final Systolic Blood Pressure During Experimental Sessions with Placebo or any MDMA Dose in MAPS-Sponsored Studies of PTSD (MP-1, MP-2, MP-4, MP-8, MP-12) 119
Table 17: Pre-drug, Peak, and Final Systolic Blood Pressure During Experimental Sessions in Controlled Hypertension Participants in MAPS-Sponsored PTSD Study MP-8 120
Table 18: Pre-drug, Peak, and Final Diastolic Blood Pressure During Experimental Sessions with Placebo or any MDMA Dose in MAPS-Sponsored Studies of PTSD (MP-1, MP-2, MP-4, MP-8, MP-9, MP-12) 121
Table 19: Pre-drug, Peak, and Final Diastolic Blood Pressure During Experimental Sessions in Controlled Hypertension Participants in MAPS-Sponsored PTSD Study MP-8 122

Table 20: Pre-drug, Peak, and Final Heart Rate During Experimental Sessions with Placebo or any MDMA Dose in MAPS-Sponsored Studies of PTSD (MP-1, MP-2, MP-4, MP-8, MP-9, MP-12) 123
Table 21: List of All Clinically Significant Changes in Laboratory Values in Two Participants from MP-2 125
Table 22: Average ALT Values at Baseline and 2-Month Follow-up After Two Experimental Sessions in Participants from MP-1 126
Table 23: Neurocognitive Function - RBANS Mean Total Scores at Baseline, Primary Endpoint, End of Stage 1, and End of Stage 2 for MP-1, MP-4, and MP-12..... 127
Table 24: Neurocognitive Function - PASAT Trial 1 and Trial 2 Mean Raw Total Scores at Baseline, Primary Endpoint, End of Stage 1, and End of Stage 2 for MP-1, MP-4, and MP-12 127
Table 25: Summary of Ecstasy Use History and Subjective Effects of MDMA Among Healthy Volunteers in Controlled Studies Conducted Without Sponsor Support... 129
Table 26: Summary of Selected Effects in Controlled Clinical Studies Comparing MDMA and Stimulants Among Healthy Volunteers Conducted Without Sponsor Support..... 133
Table 27: Pre-Study Ecstasy Use Compared to Ecstasy Use Based on Long-term Follow-up Questionnaire After All Participants Received Two to Three Blinded or Open-label Active Dose MDMA-Assisted Psychotherapy for Treatment of PTSD 136
Table 28: Reference Safety Information Based on Case Reports of Morbidity and Mortality Possibly Associated with MDMA 151
Table 29: Serious Adverse Reactions for the IMP Considered Expected for Safety Reporting Purposes in EEA Region 152

List of Appendix Tables

Appendix Table 1: Summary of Investigator-Initiated Trials with MDMA 154
Appendix Table 2: Pre-Drug, Peak, and Final Body Temperature (ºC) During Experimental Sessions with Placebo or any MDMA Dose in MAPS-Sponsored MAA-1 170
Appendix Table 3: Pre-Drug, Peak, and Final Body Temperature (ºC) During Experimental Sessions with Placebo or Full MDMA Dose in MAPS-Sponsored MDA-1 Study 170
Appendix Table 4: Pre-drug, Peak, and Final Systolic Blood Pressure During Experimental Sessions with Placebo or any MDMA Dose in MAPS-Sponsored MAA-1 Study 170
Appendix Table 5: Pre-drug, Peak, and Final Systolic Blood Pressure During Experimental Sessions with Placebo or Full MDMA Dose in MAPS-Sponsored MDA-1 Study 171
Appendix Table 6: Pre-drug, Peak, and Final Diastolic Blood Pressure During Experimental Sessions with Placebo or any MDMA Dose in MAPS-Sponsored MAA-1 Study 171
Appendix Table 7: Pre-drug, Peak, and Final Diastolic Blood Pressure During Experimental Sessions with Placebo or any MDMA Dose in MAPS-Sponsored MDA-1 Study 171
Appendix Table 8: Pre-drug, Peak, and Final Heart Rate During Experimental Sessions with Placebo or any MDMA Dose in MAPS-Sponsored MAA-1 Study 172
Appendix Table 9: Pre-drug, Peak, and Final Heart Rate During Experimental Sessions with Placebo or any MDMA Dose in MAPS-Sponsored MDA-1 Study 172
Appendix Table 10: Summary of Lifetime and Baseline Positive and Serious Responses on C-SSRS for Study MAA-1 172
Appendix Table 11: C-SSRS Positive and Serious Responses During Experimental Sessions and Integrative Session 1, Day 2 Phone Call, and Day 7 Phone Call Post-Drug for Study MAA-1 173
Appendix Table 12: C-SSRS Positive Responses at Endpoints After Treatment for Study MAA-1 174
Appendix Table 13: Summary of Lifetime and Baseline Positive and Serious Responses on C-SSRS for Study MDA-1 174
Appendix Table 14: C-SSRS Positive and Serious Responses During Experimental Sessions and 1-Day Post-Drug for Study MDA-1 175
Appendix Table 15: C-SSRS Positive Responses During Telephone Contact Following Experimental Sessions for Study MDA-1 176
Appendix Table 16: C-SSRS Positive Responses at Endpoints After Treatment for Study MDA-1 176
Appendix Table 17: Prevalence of Spontaneously Reported Reactions During Experimental Sessions and Telephone Contact on Day 1-7 After Experimental Sessions in Sponsor-Supported Phase 2 Study MAA-1 177
Appendix Table 18: Prevalence of Spontaneously Reported Reactions During Experimental Sessions in MDA-1 182
Appendix Table 19: Relative Incidence of Spontaneously Reported Reactions During Telephone Contact on Day 1-7 After Experimental Sessions in MDA-1 183

Appendix Table 20: Adverse Events by MedDRA (V. 17.1) System Organ Class (SOC) among Autistic Adults in Sponsor-Supported Phase 2 Study of MDMA-Assisted Psychotherapy MAA-1 187
Appendix Table 21: Adverse Events by MedDRA (v 17.1) System Organ Class (SOC) among Participants with Anxiety Associated with a Life-threatening Illness in Sponsor Supported Phase 2 Study of MDMA-Assisted Psychotherapy MDA-1 . 188
Appendix Table 22: Highlights of MDMA Clinical Pharmacology and Cardiac Safety 190

List of Figures

Figure 1: Chemical form of MDMA 18
Figure 2: Metabolism of MDMA in Humans 67
Figure 3: Least Squares Mean Estimates of Change in CAPS-IV from Baseline to Post 3rd Experimental Session 83
Figure 4: Least Squares Mean Change in CAPS-IV from Baseline to Long-Term Follow-Up 84
Figure 5: CSSR-S Positive Ideation in MP16 and MP17 (N=37) 114

List of Abbreviations

Ach	Acetylcholine
AE(s)	Adverse Event(s)
ALT	Alanine Aminotransferase
API	Active Pharmaceutical Ingredient
ARF	Acute Renal Failure
AVP	Arginine Vasopressin
BDNF	Brain Derived Neurotrophic Factor
bpm	Beats per minute
°C	Degrees Celsius
CAPS	Clinician Administered PTSD Scale
CBF	Cerebral Blood Flow
CL	Renal Clearance
CL/F	Oral Clearance
cGMP	Current Good Manufacturing Practice
CNS	Central Nervous System
COMT	Catechol-O-methyltransferase
C-SSRS	Columbia Suicide Severity Rating Scale
CTproAVP	Stimulating Secretion of Copeptin
DAT	Dopamine Transporters
DEA	Drug Enforcement Administration
DBP	Diastolic Blood Pressure
DIC	Disseminated Intravascular Coagulation
DMF	Drug Master File
DNA	Deoxyribonucleic Acid
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders IV
EKG	Electrocardiogram
ESR	Erythrocyte Sedimentation Rate
FDA	Food and Drug Administration
fMRI	Functional Magnetic Resonance Imaging
G-CSF	Granulocyte-colony Stimulating Factor
GD	Gestational Days
HHMA	3,4-Dihydroxymethamphetamine
HMA	4-Hydroxy-3-methoxy-amphetamine
HMMA	4-Hydroxy-3-methoxy-methamphetamine
HPA	Hypothalamus-pituitary-adrenal
HPMC	Hydroxypropylmethylcellulose
HR	Heart Rate
IB	Investigator's Brochure
IL	Interleukin
IND	Investigational New Drug
LD50	Lethal Dose in 50% of Cases
LSD	d-Lysergic Acid Diethylamide
MAO	Monoamine Oxidase
MAO-A	Monoamine Oxidase A
MAOI	Monoamine Oxidase Inhibitor
MAPS	Multidisciplinary Association for Psychedelic Studies

MDA	3,4-Methylenedioxyamphetamine
MDMA	3,4-Methylenedioxymethamphetamine
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
NET	Norepinephrine Transporter
NK	Natural Killer
PASAT	Paced Auditory Serial Addition Task
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
PMA	Paramethoxyamphetamine
PMMA	Paramethoxymethamphetamine
PND	Postnatal Day
PTSD	Posttraumatic Stress Disorder
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
SAE(s)	Serious Adverse Event(s)
SAR	Serious Adverse Reaction
SBP	Systolic Blood Pressure
SERT	Serotonin Transporter
SIADH	Syndrome of Inappropriate Antidiuretic-hormone Secretion
SNRI	Selective Serotonin and Norepinephrine Uptake Inhibitor
SPECT	Single Photon Emission Tomography
SSRI	Selective Serotonin Reuptake Inhibitor
SUD	Subjective Units of Distress
TNF-α	Tumor Necrosis Factor-alpha
VHD	Valvular Heart Disease
VMAT2	Vesicular Monoamine Transporter 2
WBC	White Blood Cell Count
8-OH-DPAT	8-Hydroxy-2-(di-n-propylamino)tetralin

1.0 Summary

The Multidisciplinary Association for Psychedelic Studies (MAPS) is a United States (U.S.)-based non-profit research and educational organization supporting research of the therapeutic potential of 3,4-methylenedioxymethamphetamine (MDMA). MAPS is the sponsor of clinical trials of MDMA-assisted psychotherapy for patients with chronic disorders such as Posttraumatic Stress Disorder (PTSD), social anxiety associated with autism, and anxiety related to terminal illnesses. In 2014, MAPS formed the MAPS Public Benefit Corporation (MPBC), a US-based wholly owned subsidiary of MAPS that has been delegated the responsibility of trial organization for all research studies within the MDMA Clinical Development Program. In 2017, MAPS initiated the establishment of MAPS Europe B.V. in the Netherlands, as a second wholly-owned subsidiary of MAPS. MAPS Europe B.V. is the designated sponsor for studies in the European Economic Area.

Findings from MAPS-sponsored Phase 2 studies indicate greater reductions in PTSD symptoms among participants who received active doses of MDMA (75 to 125 mg) plus psychotherapy compared with active control group participants who were given comparator (0 to 40 mg MDMA) plus psychotherapy, and that MDMA-assisted psychotherapy was generally well-tolerated [1-6]. Supported by these findings, MAPS has sponsored ongoing and planned Phase 1 to 3 studies of MDMA-assisted psychotherapy in people with PTSD. The program of research also includes studies of drug pharmacokinetics and startle response in healthy volunteers and mood and physiological response in a therapy setting.

MDMA-assisted psychotherapy is an experimental treatment that combines psychotherapeutic techniques with administration of MDMA under direct observation as a pharmacological adjunct that enhances psychotherapy. Prior to placement on the Drug Enforcement Administration's (DEA) list of Schedule I substances, MDMA was administered to thousands of people in psychotherapeutic practice outside of clinical trials. This Investigator's Brochure (IB) provides information on the pharmacology, safety, and efficacy of MDMA. The information presented in this IB summarizes results from published research studies of MDMA conducted by groups outside of the sponsor, sponsor collected data, and published studies and case reports of people who use Ecstasy, material represented as containing MDMA. In this document, 'MDMA' will be used to refer to drug of known purity used in a controlled setting and 'Ecstasy' will be used to describe drug-related information gathered from epidemiological settings.

PTSD is a psychiatric disorder that affects approximately 4% of the global population and over 8% of the US population [7, 8]. PTSD reduces quality of life and can affect physical health [9, 10]. Evidence based psychotherapies and pharmacotherapies exist, but may be difficult to tolerate [11-13], and are ineffective for many individuals with PTSD, with an estimated 40 to 60% of patients remaining symptomatic and meeting diagnostic criteria even after receiving treatment [13-15]. In addition, available pharmacotherapies used to treat PTSD may have problematic side effects and generally require long-term and/or consistent use to maintain effectiveness [12]. Novel interventions are needed to better treat people with PTSD. MDMA-assisted psychotherapy might also serve as a

tolerable treatment that requires only a handful of administrations with lasting treatment effects.

MDMA is a ring-substituted phenethylamine also known as methylenedioxymethamphetamine. MDMA is structurally similar, but functionally distinct, from amphetamines. MDMA is a chiral molecule and the hydrochloride salt of racemic anhydrous MDMA is under development for marketing. The drug product is formulated as a white crystalline powder compounded with excipients and placed in capsules. The hydrochloride salt of MDMA is readily water soluble and is lipophilic once ionized. Estimates from animal data suggest a median lethal dose (LD50) in humans between 10 to 20 milligram per kilogram (mg/kg) [16]. Due to a wide range of responses to identical dosing [17], the sponsor's human trials use fixed doses equivalent to between 1 and 4 mg/kg (active doses in studies range from 75 mg to 225 mg). Onset of MDMA effects occurs 30 to 60 minutes after oral administration [18, 19], peak effects appear 75 to 120 minutes post-drug [17, 20-22], and duration of effects lasts from 3 to 6 hours [20, 21, 23], with most effects returning to baseline or near-baseline levels 6 hours after drug administration. The elimination half-life of active doses of MDMA is 8 to 9 hours [24].

The pharmacokinetics of MDMA in humans has been characterized using oral doses of up to 150 mg MDMA, and disposition follows nonlinear pharmacokinetics. Metabolism of MDMA results in N-demethylation to 3,4-methylenedioxyamphetamine (MDA). The parent compound and MDA are further O-demethylated to 3,4-dihydroxymethamphetamine (HHMA) and 3,4-dihydroxyamphetamine (HHA), respectively. Both HHMA and HHA are subsequently O-methylated mainly to 4-hydroxy-3-methoxy-methamphetamine (HMMA) and 4-hydroxy-3-methoxy-amphetamine (HMA). These four metabolites, particularly HMMA and HMA, are known to be excreted in the urine as conjugated glucuronide or sulfate metabolites [24].

MDMA concomitantly promotes release, inhibits reuptake, and extends duration of serotonin, norepinephrine, and dopamine in the synaptic cleft to increase serotonergic, noradrenergic, and dopaminergic neurotransmission. MDMA is a triple monoamine reuptake inhibitor, and similar drugs in this class have been found to exert potent anti-depressant activity with a favorable safety profile in clinical trials [25, 26]. MDMA produces anxiolytic and prosocial effects through release of the monoaminergic neurotransmitters, with the greatest effect on serotonin, followed by norepinephrine and dopamine [27-31]. Subjective effects of MDMA can include increased compassion for self and others, reduced defenses and fear of emotional injury, and making unpleasant memories less disturbing while enhancing communication and capacity for introspection [32-35]. These factors taken together 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 might make MDMA a suitable pharmacological adjunct to enhance psychotherapy for treatment of anxiety disorders, such as PTSD, social anxiety in autistic adults, and anxiety associated with other conditions. Published results from a MAPS-sponsored Phase 2 clinical trial of MDMA-assisted psychotherapy for PTSD in

Charleston, South Carolina (MP-1) showed clinically and statistically significant improvements in PTSD severity (N=23) [3]. Findings from the long-term follow-up of MP-1 suggest that therapeutic benefits were sustained for an average of 41 months post-treatment [4]. The sponsor's second Phase 2 pilot study conducted in Switzerland (MP-2) demonstrated clinically significant improvements in PTSD symptoms in the 125 mg MDMA dose group but was not statistically different than the 25 mg MDMA dose group (N=14) [5]. Long-term Follow-up data 12 months later suggest that therapeutic benefits continued to increase in this subject population. There were no possibly or probably drug-related Serious Adverse Reactions (SARs) or safety concerns in either study. Subsequently, safety findings from initial studies were confirmed in five Phase 2 PTSD studies. These include a dose-response study in military veterans, firefighters and police officers (N=26, MP-8) [2], in Charleston, SC; another dose-response study conducted in Boulder, CO, among people with trauma from any cause and, employing multiple therapist teams (N=28, MP-12) [6]; an active-controlled study conducted in Israel (N=10, MP-9); a placebo-controlled study conducted in Canada (N=6, MP-4), and an open-label Phase 1/Phase 2 pilot study of a combination of MDMA-assisted psychotherapy with a form of conjoint cognitive behavioral therapy geared toward dyads (N=12, MPVA-1)[36]. Safety findings for other indications were corroborated in a Phase 2 social anxiety study in autistic adults (N=12, MAA-1) [37, 38], and a Phase 2 anxiety study in participants with a life-threatening illness (N=21, MDA-1). (See Table 4: Summary of Completed Sponsor Supported Studies with MDMA)

Data from MAPS studies and from publications from other researchers published literature show that MDMA produces sympathomimetic effects that include significant transient, self-limiting increases in heart rate (HR) and blood pressure that were well-tolerated by healthy individuals [3, 5, 17, 19-21, 39-43]. Most people did not experience elevations that exceeded those seen after moderate exercise. These results were reproduced in an investigator-sponsored Phase 1 safety study [44]. Risks posed by elevated blood pressure were addressed by excluding candidates with a history of cardiovascular, cerebrovascular disease, or with pre-existing uncontrolled hypertension, and by regularly monitoring blood pressure and pulse throughout Experimental Sessions. Common reactions from MDMA reported in the literature and clinical trials were transient and diminished as drug effects waned during the session and over the next one to 7 days.

MDMA may reduce responsiveness to changes in water/salt balance after normal and increased water consumption [45]. Common adverse effects of an active dose of MDMA include anxiety, tight jaw or bruxism, headache, fatigue, lack of appetite, dizziness, insomnia, impaired gait or balance, and muscle tightness (see Section 6.4.1 Adverse Events). Suicidal ideation has been observed in blinded PTSD studies and is under evaluation as an Adverse Event of Special Interest. MDMA is also a mild immunosuppressant [46].

As of April 30, 2020, with 279 individuals exposed to MDMA in the development program across various indications and at least 1,431 participants in MDMA research studies conducted without sponsor support, the sponsor has observed an acceptable risk-benefit ratio for MDMA-assisted psychotherapy. There have been no unexpected Serious Adverse Reactions (SARs) to date and Serious Adverse Events (SAEs) have been rare.

The most commonly reported adverse events (AEs) in a pooled analysis of six Phase 2 studies were psychiatric symptoms, most commonly anxiety, depressed mood, irritability, and panic attacks. Participants reported experiencing anxiety, dizziness, fatigue, headache, jaw clenching/tight jaw, lack of appetite, and nausea during MDMA-assisted sessions [1]. Most AEs were mild to moderate and lasted no longer than 7 days. As of April 30, 2020, a single expected SAR (increased ventricular extrasystoles), has been reported in MAPS-sponsored clinical trials.

A pooled analysis of blinded Phase 2 subjects (N=103) found a large effect size between treatment groups (d=0.8) with a low overall dropout rate (7.6%) [1]. A long-term follow-up of participants at least 12 months later found a low relapse rate (12.1%) to support benefits outweighed risks associated with treatment [47]. PTSD is a serious, chronic, life-threatening condition that afflicts a substantial number of individuals who are more likely to exhibit increased risk of suicide, psychiatric comorbidities, cardiovascular disease, and functional impairment. Those who suffer from PTSD are often insufficiently treated with available therapies. In MAPS' clinical trials to date, MDMA has been well-tolerated and has reduced symptoms of PTSD. In summary, results from clinical studies to date suggest a favorable risk/benefit profile among PTSD subjects treated with a two to three-session MDMA-assisted psychotherapy, which also included follow-up non-drug psychotherapy sessions. Therefore, MDMA-assisted psychotherapy might be a novel treatment option with the potential for sustained improvements after only a handful of sessions.

2.0 Introduction

MDMA is not a novel compound. It was first synthesized and patented by Merck in 1912 [48] and is currently not covered by a patent. MAPS holds the Drug Master File (DMF) and an Investigational New Drug (IND) file for MDMA with the U.S. Food and Drug Administration (FDA). After MDMA was rediscovered by the chemist Alexander Shulgin in 1976 [49], he and his colleagues provided initial reports of its pharmacology, with 80 mg to 160 mg MDMA required to produce desired subjective effects in humans [50, 51]. MDMA was found to robustly influence human emotional status in a unique way [51] without adversely affecting physiological functions or perception, such as visual perception or cognition [18, 20, 22, 23].

MDMA possesses a complex pharmacological profile that is dominated by its effects as a monoamine releaser and reuptake inhibitor, with additional effects on limiting neurotransmitter production and degradation. Its prominent effects on serotonin differentiate it from amphetamine and methamphetamine, which primarily act on norepinephrine and dopamine pathways [27, 52]. In the Merck Index, MDMA resides in the Entactogen class [53]. Entactogens contain a ring-substituted amphetamine core, belong to the phenethylamine class of psychoactive drugs, and are described as promoting acceptance and compassion for self and others, changing recognition and response to emotions, and increased interpersonal closeness [33, 54-56]. In comparison to anxiolytics, antidepressants and atypical antipsychotics, steady state levels in blood are not required for MDMA to function as a catalyst to psychotherapy.

Shulgin and Nichols were the first to report the effects of MDMA in humans [51]. Reported effects of MDMA include enhanced feelings of closeness to others, well-being,

and insightfulness [57-59]. MDMA was used in the 1970s and 1980s to enhance psychotherapy for individuals, couples, and groups to treat various psychological disorders, including moderate depression and anxiety [58, 60-62]. It was also found to be useful in reducing physical pain secondary to certain kinds of cancer [61]. No formal controlled clinical trials of safety and efficacy were conducted at the time [58, 63].

During the early 1980s, increasing numbers of people began using MDMA, sold as 'Ecstasy', outside of therapeutic contexts [64]. In the U.S., an estimated 6.8% of people aged 12 years and above reported using 'Ecstasy' (material represented as containing MDMA) at least once in their lifetimes [65], and an estimated 4% of Europeans aged 15 to 64 reported lifetime Ecstasy use [66].

MDMA was added to the list of Schedule I controlled substances in the U.S. in 1985, defining it as a drug with a high potential for abuse and no accepted medical use [67, 68]. Classification as a Schedule I controlled substance, combined with the early research in animals and recreational users, hampered clinical research for medical uses of MDMA until the 1990s. Reports of AEs following use of Ecstasy have raised safety concerns regarding MDMA administration, including hyperthermia [69-71], changes in serotonin transporter (SERT) density, and impaired memory and executive function [72-76]. However uncontrolled studies of Ecstasy use and nonclinical animal studies that use inappropriately high exposures of MDMA yielded findings that are open to an array of interpretations [77, 78]. The vast majority of publications on Ecstasy users are retrospective reports in polydrug-users [79, 80].

Initial human studies from the 1990s focused on physiological effects of MDMA from a safety perspective, and current investigations have examined the effects on attention, prosocial effects, memory and brain activity, and human drug discrimination. Findings from an initial sponsor-funded study indicated that MDMA-assisted psychotherapy could be conducted safely in people with chronic PTSD who had failed first line treatments [81]. This was demonstrated in a chronic, treatment-resistant PTSD sample in a sponsored placebo-controlled study (MP-1) [4], which demonstrated durable improvement in PTSD severity. In this study, MDMA had no deleterious effects on cognitive function when given on two occasions, spaced 1 month apart. In addition, placebo-controlled Phase 1 clinical trials confirmed that the active doses of MDMA produce an easily controlled state characterized by euphoria, increased well-being, sociability, self-confidence, extroversion, transient increases in anxiety, and minor alterations in perception [18, 20-22, 82-86].

MAPS has completed six Phase 2 investigations of MDMA-assisted psychotherapy for treatment of PTSD (see Table 4: Summary of Completed Sponsor Supported Studies with MDMA). The pooled Phase 2 efficacy results in PTSD participants indicate that MDMA-assisted psychotherapy administered in a controlled clinical setting demonstrated that the treatment was safe and efficacious among patients with moderate to severe PTSD [1, 47]. Durable improvements were found at least 12 months after the last Experimental Session in 91 participants who received a therapeutically active dose of MDMA in these studies, and 67% did not meet PTSD diagnostic criteria per CAPS-4 assessment [47]. Though the interpretation of long-term results might be limited due to a lack of a blinded control group at this time point, the results suggest significant durable improvement in PTSD

symptoms that lasted for at least 12 months for many participants following MDMA-assisted psychotherapy. A report from a pilot study of a combination of MDMA-assisted psychotherapy with a form of conjoint cognitive behavioral therapy geared toward dyads is now complete (MPVA-1) [36], and two open-label Phase 2 PTSD studies testing the same dosing regimen employed in Phase 3 trials are near completion, and the data are undergoing final review (MP16 and MP17). These Phase 2 clinical studies in subjects with PTSD supported the initiation of Phase 3 clinical studies for treatment of PTSD with MDMA-assisted psychotherapy [87]. Planned Phase 2 studies include three investigations of MDMA-assisted psychotherapy for people with PTSD in Europe and the U.S. The studies to take place in Europe are intended to prepare sites in Europe for Phase 3 studies.

The first of two Phase 3 randomized, double-blind, placebo-controlled MDMA-assisted psychotherapy trials commenced in November 2018 at approximately fifteen study sites in the U.S., Canada, and Israel and as of April 30, 2020, 90 subjects were treated in at least 1 blinded Experimental Session (see Table 5 Summary of Ongoing and Planned Sponsor-Supported Trials with MDMA).

Additional MDMA research studies supported by the sponsor include a randomized, placebo-controlled, double-blind study of the effects of 100 mg MDMA on startle response, a study of MDMA pharmacokinetics in healthy volunteers and people with impaired liver function, and a study of the effects of fasting on MDMA pharmacokinetics (see Table 5).

Based on clinical experience with PTSD, MAPS is currently exploring additional indications for this treatment that share anxiety as an element or feature of the condition, or that may benefit from a greater ability to confront emotional thoughts and memories. Two studies have been completed exploring the use of MDMA-assisted therapy for social anxiety in autistic adults) and MDMA-assisted psychotherapy to address anxiety associated with a life-threatening illness. A planned Phase 2 investigation of the safety and effectiveness of MDMA-assisted psychotherapy for treatment for people with eating disorders is also underway.

This IB will present available nonclinical and clinical and epidemiological data on MDMA collected up through 31 March 2020 and on data collected from sponsor-initiated studies up through 30 April 2020. The risk/benefit profile remains consistent since the last edition of this IB.

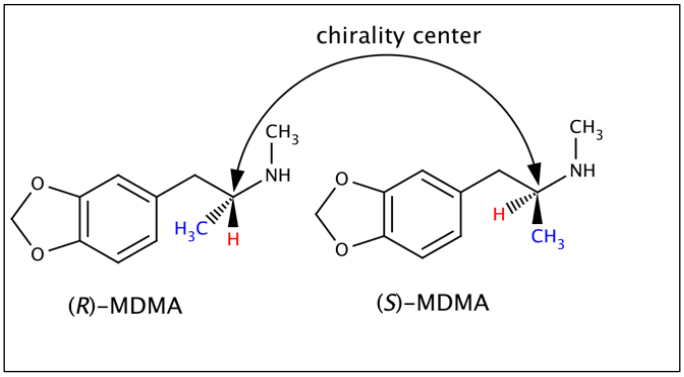
3.0 Physical, Chemical, and Pharmaceutical Properties and Formulation

MDMA is the short form of the name 3,4-methylenedioxymethamphetamine. The International Union of Pure and Applied Chemistry (IUPAC) nomenclature is (RS)-1-(benzo[d][1,3]dioxol-5-yl)-N-methylpropan-2-amine, and the United States Adopted Name (USAN) is midomafetamine hydrochloride.

MDMA is structurally similar, but functionally distinct, from amphetamines and mescaline. MDMA, also known as 3,4-methylenedioxy-N-methylamphetamine and N-methyl-3,4-methylenedioxyamphetamine, has the chemical formula of $C_{11}H_{15}NO_2$.

MDMA is a chiral molecule, possessing two enantiomers, S(+)-MDMA and R(-)-MDMA, with S(+)-MDMA being more potent than R(-)-MDMA [16, 88]. Research in humans to date and the majority of nonclinical studies have used racemic MDMA, or an admixture containing equal amounts of both enantiomers.

Figure 1: Chemical form of MDMA



The sponsor is developing the racemic anhydrous hydrochloride salt of MDMA for marketing. The salt of MDMA is readily water soluble with a pKa of 9.9 [89], which influences whether it is ionized in plasma and slightly reduces its ability to cross into oral fluid. MDMA is also more lipophilic, which drives it into oral fluid, and may influence its ability to pass the blood brain barrier and influence signaling in the central nervous system (CNS) [90].

Sponsor-supported early Phase 1 and 2 studies in the U.S. used MDMA manufactured in 1985 by David Nichols, Ph.D., at the Department of Medicinal Chemistry and Pharmacology, Purdue University, West Lafayette, IN. The MDMA was manufactured as a single lot for use in FDA-regulated clinical trials. The most recent analysis of drug stability and purity conducted in June 2020 confirmed that this MDMA is 99.9% pure with no detectable decomposition. Studies conducted outside of the U.S. use MDMA from a single batch manufactured in 1998 by Lipomed AG in Arlesheim, Switzerland.

In November 2018, the sponsor released a clinical batch of Investigational Medicinal Product (IMP) manufactured according to current Good Manufacturing Practices (cGMP), and all subsequent sponsored studies follow this standard. The drug substance manufacturer is Onyx Scientific, Ltd in the United Kingdom and the drug product manufacturer is Sharp Clinical Services in the U.S. The synthetic route uses achiral methods. Up to 24 months stability data are available on this batch of MDMA drug substance, stored at 25°/60%RH and up to 6 months data at both 30°/65%RH and 40°/75%RH. No significant degradation has been detected under any of these conditions.

MDMA in the form of white crystalline powder is compounded with inert material and formulated in hydroxypropylmethylcellulose (HPMC) capsules of 40 and 60 mg MDMA hydrochloride with excipients mannitol and magnesium stearate. Placebo to match consists of mannitol and magnesium stearate. Initial and supplemental doses are comprised of administering two 40 mg or two 60 mg capsules; supplemental doses consist of a single capsule of either inactive placebo, 40 or 60 mg MDMA. Up to 12

months data are available on capsules stored at 25°/60%RH and up to 3 months data on capsules stored at 40°/75%RH. Apart from some isolated examples of delayed dissolution, which are not believed to be stability-related, no degradation and no adverse stability effects have been observed. In order to provide data to support evaluation of more extreme temperature deviations during shipping, the stability of the capsules has been studied for 1 week at both -20° and 50°/75% RH. No degradation or adverse effects were seen on the capsules.

MDMA does not require special conditions for storage. In batches produced under cGMP, the drug product is stored in aluminum cold-formed blister strips or in HDPE bottles placed in a dark safe at room temperature in a dry, clean, well-ventilated space at temperatures between 15 to 30°C, and short term deviations between 5 to 30°C are allowed on the basis of available stability data. As a Schedule I controlled substance, MDMA is stored and handled in compliance with relevant federal or national, state, provincial and local regulations. In accordance with the requirements of the U.S. DEA and international drug regulatory authorities, license holders are responsible for storing and dispensing the MDMA, and ensuring it is stored under appropriate protections.

MDMA doses in sponsor-supported early Phase 1 and 2 studies are fixed within the therapeutic dose range of 75 mg to 125 mg, rather than based on body weight, based on initial publications information and lack of linear dose response with behavioral effects in Phase 1 and sponsor-supported studies [17]. The clinical dose tested in Phase 3 trials is a flexible dose ranging from 80 mg to 120 mg, which is equivalent to 1.1 mg/kg to 1.8 mg/kg in the initial dose for a 70 kg person. Doses of MDMA produced for MAPS' research have included 20, 25, 30, 40, 60, 75, 80, 100, 120, and 125 mg. Supplemental doses included doses of 0, 12.5, 15, 37.5, 50, and 62.5 mg. Low doses of MDMA were used in Phase 2 studies as a comparator, and ranged from 25 mg to 40 mg, and lactose was used as placebo. Lactose has been used in most Phase 2 studies as an inactive excipient and placebo to match on the basis of similar properties and was selected because it can be safely consumed by most people. All Phase 3 and most of the Phase 1/ Phase 2 studies after 2018 used mannitol and magnesium stearate as excipients and for corresponding placebo.

4.0 Nonclinical Studies

4.1 Nonclinical Pharmacology

Findings from nonclinical animal and in vitro research are presented. 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 intending to develop chemical incapacitants or means of enhancing interrogation [91]. Investigations of the pharmacology, functional effects, and toxicity of MDMA in animals have generally included injections of large and often repeated doses of MDMA that are not human-equivalent doses. Studies of MDMA have been conducted in primates and rodents. Primate species studied include baboon, macaque, rhesus monkey, and squirrel monkey, and rodents include mice and rats. Studies of circadian rhythm have occurred in hamsters [92]. Beginning in the mid-2000s onwards, reports re-examining these effects have

questioned the applicability of allometric interspecies scaling models for MDMA [77, 93, 94].

MDMA possesses a complex pharmacological profile that is dominated by its effects as a monoamine releaser and reuptake inhibitor. Its prominent serotonergic effects differentiate it from amphetamine and methamphetamine, which primarily act on dopamine and norepinephrine [27, 52]. MDMA also has a complex profile from a pharmacokinetics perspective and has been demonstrated in multiple animal models to follow nonlinear pharmacokinetics, with increased doses resulting in disproportionate increase in exposure to the parent compound (see Section 4.2 Pharmacodynamic and Product Metabolism in Animals). Additionally, MDMA exhibits pharmacodynamic drug interactions with other drugs commonly used in psychiatry. In the following sections, the pharmacology of MDMA is presented based on nonclinical animal studies from both primary literature and sponsor conducted studies.

A full listing of planned, ongoing and completed nonclinical studies conducted by MAPS is available below (Table 1):

Table 1: Summary of Completed and Planned Nonclinical Toxicology Studies

Species	Type of Study	Findings (when available) and Notes	Study Code/ Completion Date (* =in progress)
Rat	28-Day General Toxicology	↓ weight gain ↓ ♀ urine pH, blood: BUN, Glu, Creatinine, LDH, (♀,♂) Cl ↑ (♀,♂) WBC, Phos (trend)	EMD-SC-002/ 1986[95, 96]
Dog	28-Day General Toxicology	↓ weight gain 9, 15 mg/kg ↓ testicle size ↑ prostate size Deaths at 15 mg/kg	EMD-SC-001/ 1986[95, 96]
In vitro bacteria	†Genotoxicity Ames test	Negative for mutagenic activity ± metabolic activation	01244001/ 2020
In vitro CHO cells	†Genotoxicity Chromosome Aberration test	Negative for clastogenic activity *in vitro* ± metabolic activation	01244004/ 2020
Rat	†Genotoxicity *In vivo* Micronucleus Evaluation by Oral Gavage	Negative for clastogenic activity and disruption of mitotic apparatus *in vivo* at MTD 100 mg/kg/day, 2 days, single housing	2884-016/ 2020
In vitro HEK-hERG	†hERG Channel Inhibition patch clamp assays per ICH S7A/S7B	Negative: IC_{50} of 206 µM (~170x over clinical C_{max}); Hill coefficient=1.1	191028/ 2020
Rat	†Pilot Prenatal Developmental Toxicity Study	Well tolerated by time-mated ♀at 20 mg/kg/day p.o. GD6-17. no effect on ovarian/uterine implantation, mean gravid uterine weights, or fetal body weights. No external malformations or developmental variations in any fetus at GD21 TK: No systemic accumulation with repeated doses	2884-005/ 2020

Rabbit	†Pilot Prenatal Developmental Toxicity Study	Well tolerated by time-mated ♀at 10 mg/kg/day p.o. GD7-19, deaths at 15 and 20 mg/kg/day. At tolerated dose, no effect on ovarian/uterine implantation, mean gravid uterine weights, or fetal body weights. No external malformations or developmental variations in any fetus at GD29. TK: systemic accumulation with repeated doses	2884-006/ 2020
Rat	†Reproductive Toxicology: Fertility/Early Embryonic Development Study	NOAEL dose 10 mg/kg/day p.o. for maternal, paternal reproductive performance and fertility	2884-003/ 2020
Rat	†Reproductive Toxicology: Embryo-Fetal Development Study	*Note:* includes toxicokinetics	2884-004/ 2020*
Rabbit	†Reproductive Toxicology: Embryo-Fetal Development Study	*Note:* includes toxicokinetics	2884-007/ 2020*
Rat	†Extended Single-dose 28-Day Neurotoxicology Study	*Note:* includes toxicokinetics	2884-001/ 2020*
Dog	†Extended Single-dose 28-Day Neurotoxicology Study	*Note:* includes ECG and toxicokinetics	2884-002/ 2020*

† =Studies conducted by Charles River Labs

4.1.1 Primary Pharmacodynamics

Most effects of MDMA likely arise directly from monoamine reuptake inhibition and release, and indirectly from activation of downstream monoamine receptors and subsequent secretion of neuromodulators oxytocin and arginine vasopressin (AVP). MDMA binds primarily to membrane-bound monoamine transporters, which remove monoaminergic neurotransmitters from the space between neurons, known as the synaptic cleft. MDMA appears to alter the conformation of the transporters, enabling monoamines to diffuse out of the neuron rather than being actively transported into the presynaptic neuron [52, 97-99]. MDMA prevents the reuptake of serotonin, and to a lesser extent, norepinephrine and dopamine, and facilitates release of these neurotransmitters [52, 100-102]. The selectivity of MDMA for specific monoaminergic neurotransmitters is species-dependent and cannot solely be attributed to differences in binding affinity for specific reuptake transporters observed in vitro, as described below. In in vitro studies, MDMA was also found to compete with monoamines for sites on the vesicular monoamine transporter-2 (VMAT2), suggesting MDMA also promotes active release of monoamines from vesicular stores, in addition to inhibiting reuptake [103-105].

MDMA can inhibit monoamine oxidase A (MAO-A) in vitro at high concentrations, which preferentially degrades serotonin, and leads to accumulation of extracellular serotonin in the synaptic cleft [106, 107]. Inhibition of MAO-A may have played a role in fatalities and medical emergencies seen after combining Ecstasy with monoamine oxidase inhibitors (MAO-I) in epidemiological settings [108, 109]. Spurred on by prior reports hypothesizing that apparent greater serotonergic toxicity of MDMA in primates,

as compared to rodents, could be attributed to greater SERT affinity [110], researchers specifically examined affinity in cells transfected to express human monoamine transporters [102, 111]. These studies found that even though binding affinity of MDMA for the human norepinephrine transporter (NET) exceeded the affinity for SERT and dopamine transporters (DAT), serotonin was preferentially released over norepinephrine and dopamine [102], which may account for primarily serotonergic effects of MDMA. On the other hand, in rodents MDMA affinities for transporters are ordered as SERT>NET>DAT [112]. MDMA does not have as strong an affinity for the DAT as methamphetamine [27].

The ability of MDMA to stimulate release of pre-synaptic serotonin, norepinephrine, and dopamine in multiple brain regions and inhibit reuptake has been well documented [113]. In vivo microdialysis and voltammetry results show significant enhancement of serotonin, and to a lesser extent dopamine following MDMA administration, a response attenuated by various transporter inhibitors. MDMA-stimulated serotonin and dopamine release has been measured in the striatum, nucleus accumbens, prefrontal cortex (PFC), and the hippocampus of freely moving rats [114-118], including after administering 0.32 to 3.2 mg/kg MDMA [118]. Female rats exhibited longer duration of nucleus accumbens dopamine, and longer duration of serotonin after 1 and 3.2 mg/kg MDMA. In addition, enhancement of Acetylcholine (Ach) release has been demonstrated in the PFC, striatum, and hippocampus by both a dopaminergic and serotonergic dependent mechanism [119, 120]. The subjective and physiological effects of MDMA are produced by the dynamic interaction of these transmitter systems on numerous brain networks that modulate learning and memory, emotion, reward, attention, sympathetic/parasympathetic activity, and neuroplasticity.

In addition to carrier-mediated monoamine release, MDMA has affinity in vitro for specific serotonin, norepinephrine, acetylcholine, and histamine receptors, although the concentrations tested may not translate to standard human MDMA doses [30, 121-123]. An in vitro binding study comparing MDMA with several drugs that include cathinone derivatives suggests that contrary to an earlier report of low affinity for 5HT2A serotonin receptors, MDMA may have significant effects at the receptor [31]. MDMA likely modulates 5HT1A receptors indirectly through serotonin release, though it is possible that MDMA may also act as a partial 5HT1A agonist in some brain areas [124]. Findings from other studies suggest that MDMA shares qualities with 5HT1A agonists. Early studies in rats suggest that pharmacological activation of 5HT1A receptors reduce anxiety and aggression [125, 126], and some drug discrimination studies suggest that the 5HT1A agonist 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) at least partially substitutes for MDMA [127-129].

Findings from drug discrimination studies in rats suggest dose-dependent differences in the role of the serotonergic versus the dopaminergic system, with rats trained on 1.5 mg/kg MDMA recognizing SSRIs as similar while rats trained on 3.0 mg/kg recognized amphetamine as similar, and rats trained on both doses recognizing 5HT1A-related compounds as similar. Training with 1.5 mg/kg but not 3.0 mg/kg MDMA resulted in considering higher doses of a 5HT2A agonist as similar [130]. The same research team determined that dopamine antagonists interfered with the stimulus properties of amphetamine, but not MDMA [131].

4.1.2 Secondary Pharmacodynamics

MDMA has been shown to have a diverse array of secondary pharmacodynamics in animals. Both enantiomers of MDMA enhance Ach release in the PFC [120, 132] and promote changes in GABAergic systems that correlate with sociability [133]. There is some evidence that 5HT2B receptors are involved in stimulating increased locomotor activity in mice, reported in studies administering 20 mg/kg [134]. At least some direct or indirect effects of MDMA on serotonin receptors may alter GABA uptake in the ventral tegmental area of rats [135]. An in vitro study found that S-MDMA showed signs of competitive interaction with the alpha-4 beta-2 nicotinic receptor which are implicated in learning [136], while R-MDMA did not produce this effect [137].

Infusion of serotonin in the rat brain stimulates secretion of oxytocin into peripheral blood via activation of 5HT1A, 5HT2C, and 5HT4 receptor subtypes, as well as AVP secretion via activation of 5HT2C, 5HT4, and 5HT7 receptor subtypes [138]. MDMA was shown to increase oxytocin and AVP secretion in rats [139] through a 5HT1A mechanism [140, 141]. MDMA also promotes norepinephrine release through reuptake inhibition, which is an additional pathway that can contribute to oxytocin secretion and may control emotion regulation. Both oxytocin and AVP are implicated in the widespread regulation of behavioral aspects of mood and act on different target organs to modulate physiological functions in the periphery [142]. Drug-discrimination and pre-pulse inhibition studies in rats lacking a SERT gene confirm the importance of the serotonin transporter in the interoceptive effects of 5 or 10 mg/kg MDMA, and its enhancement of pre-pulse inhibition [143].

In rats, 10 or 20 mg/kg doses of MDMA elevated serum corticosterone (a rodent cortisol analog) and prolactin [144-146], with elevations lasting up to 4 hours after dosing, and with hormone levels attenuated by a 5HT2A serotonin receptor antagonist. Given the dosage used was five to 10.7 times larger than an active dose in humans, it is unclear if this response is analogous to elevated cortisol in humans or whether it reflects a different process. Administering 1 to 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 [29]. 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 indirect action on 5HT2A receptors by R(-) -MDMA [147].

MDMA has been shown to have significant effects outside the central nervous system; namely on the cardiovascular, osmoregulatory, and immune systems. MDMA has been shown to cause increases in blood pressure and heart rate in small mammals and primates. These effects are possibly controlled through increased sympathomimetic activity via beta adrenergic receptors [98, 148, 149]. For further information on the cardiac effects in animals see Section 4.1.3.2 Cardiovascular System. MDMA has also been shown to effect water regulation by activation of the AVP system [150], thus explaining the increased thirst seen in humans. For more information on the mechanism of the osmoregulatory effects of MDMA see Section 4.1.3.5 Renal System. Additionally,

MDMA has been observed to have some mild immunosuppressant effects in animals. Possible mechanisms include central regulation via the HPA axis and suppression of various circulating cytokines and interleukins. For more information see Section 4.3.6.1 Immunological Effects.

4.1.3 Safety Pharmacology

Safety pharmacology studies are defined as those studies that investigate the potential undesirable pharmacodynamic effects of a substance on physiological functions in relation to exposure in the therapeutic range and above. The purpose of the safety pharmacology core battery is to investigate the effects of the test substance on vital functions. Safety pharmacology studies were conducted with the racemic mixture of the parent compound, as the finished product formulations for clinical usage do not substantially alter the pharmacokinetics and/or pharmacodynamics of the active substance.

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 [91]. LD50 may vary across strains, sexes, and housing conditions [151-153]. For example, LD50 in mice housed together is 20 mg/kg, which is considerably lower than in isolated animals [154, 155]. Considerable variation across studies in environmental factors, that are often underspecified in published reports, contribute to challenges in extrapolating findings in animal studies to humans.

The majority of these studies employed multiple dosing regimens to account for the shorter drug half-life in animals compared to humans, with doses ranging from 5 mg/kg to 20 mg/kg, via s.c., i.p., oral, or gavage administration. Frequently, doses are administered at regular intervals of two to four times per day. Other regimens employ these doses once daily for 5 or 7 days. Doses were selected through use of simple dose conversions or allometric scaling, a method of modeling human equivalent doses in other species [156]. Comparison of pharmacokinetic parameters requires consideration of route of administration for dose conversions between species (see Table 2 Pharmacokinetic Constants for Plasma MDMA After Various Routes of Administration to Humans or Animals).

4.1.3.1 Central Nervous System

Most nonclinical research with MDMA has focused on the Central Nervous System (CNS) effects on serotonergic neurons, while other studies have examined changes in neurohormones or effects on neuroplasticity. It appears that single doses of MDMA (2.5 mg/kg i.p. in monkeys, 7.5 mg/kg i.p. in rats), approximately four times a human equivalent dose based on exposure levels, reduces brain serotonin production for 2 weeks or more [93] but does not increase validated markers of neurotoxicity associated with neurodegeneration [94]. 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 [157]. One report detected a reduction in N-acetylaspartate to creatine ratio, which the authors considered a sign of neuronal injury,

although no decreases in brain serotonin were detected after administration of two 1 mg/kg doses of MDMA to rhesus monkeys for 2 days [158].

Studies in rodents and primates suggest that repeated high doses of MDMA could reduce regional serotonin, damage serotonin axons and cause neurotoxicity [98, 110, 159-164] and promote apoptosis in the hippocampus after 5 or 10 mg/kg MDMA given daily for a week, but not after 2.5 mg/kg [165]. Serotonin syndrome is defined as an excess of serotonin in the CNS causing a suite of specific signs and symptoms that can require intervention [166-168]. Doses of 10 mg/kg administered s.c. and i.p., but not 2 mg/kg, produced signs of serotonin syndrome in rats, but neither dose reduced total serotonin levels in the brain 2 weeks after drug administration. Serotonin syndrome severity correlates with MDMA plasma concentrations [77]. MDMA doses up to 2.5 mg/kg appear to alter regulation of serotonergic signaling in the rat brain without producing damage to serotonin axons, based on transient reductions in brain serotonin and SERT levels, in the absence of indicators of neuronal injury or decreased expression of the SERT gene [78]. A study in monkeys that counted rates of different types of neural progenitor cells combined with immunohistochemistry detected signs of reduced neurogenesis, but no signs of apoptosis, in the hippocampi after an intermittent regimen of ascending doses of MDMA from 0.5 to 2.5 mg/kg approximately every 2 weeks for up to 10 months when compared with controls who did not receive MDMA [169]. This study used markers for Ki-67 cells, a type of activity dividing neural progenitor cells (NPCs), in the hippocampus, and cell death was measured via examining numbers of cells and caspase activation. The clinical dosing regimen for MDMA is up to 3 single-dose administrations with doses spaced 1 month apart, which is more similar to this primate study.

In a MAPS-sponsored pilot repeated dose 13-day toxicity study (EMD-AT-001), using tested increasing doses ranging from 25 mg/kg to 300 mg/kg, and found no changes in the brain tissue of treated rats compared to controls. The subsequent definitive 28-day repeated dose toxicity study in rats [96] found vacuolar changes in the brainstem adjacent to the trigeminal nuclei in one of ten animals receiving 50 mg/kg of MDMA and similar lesions in five of ten male rats receiving 100 mg/kg [96]. No lesions were observed in female animals. The definitive 28-day repeated dose toxicity study in dogs [170] also found lesions in the CNS of MDMA-treated dogs with doses of 3, 9, and 15 mg/kg, however the presence of the lesions was not dose-dependent, suggesting that they could be background events. These lesions included white matter changes, neural malacia and cellular infiltrates of the cerebrum. Neural chromatolysis was observed in the brainstem. The pathogenesis of these changes was unknown.

A MAPS-sponsored follow-up neurotoxicity study administering Sprague-Dawley rats 40 mg/kg or 80 mg/kg of MDMA twice a day for 4 days showed no morphological brain changes (EMD-SC-003). Neurochemical brain changes related to MDMA administration included a 50% decrease in serotonin (5-HT) and 5-Hydroyindoleacetic acid (5-HIAA) at both dosing levels. This decrease was apparent both 2 and 4 weeks after treatment. A temporary 34% decrease in homovanillic acid (HVA) was observed in the 80 mg/kg group at 2 weeks after treatment. Four weeks after treatment the HVA levels had returned to normal. These findings indicate that several, high dose administrations of MDMA produce long-term reductions (4 weeks) in 5-HT and 5-HIAA in the rat while having no

apparent effect on the dopaminergic system [170]. These studies will be supplemented with extended single-dose 28-day neurotoxicity studies in the rat and the dog to conclusively study neurotoxicity with modern experimental methods (see Table 5 Summary of Ongoing and Planned Sponsor Supported Trials with MDMA).

Motor Activity

MDMA produces some repetitive behavior in rodents, but not to the same degree as psychostimulants. MDMA has been shown to increase locomotor activity [141]. Rats on MDMA walk around a cage perimeter, interpreted as an indicator of thigmotaxis, which is a sign of anxiety [98]. However, it is notable that a 2007 publication failed to find thigmotaxis in rats given 5 mg/kg MDMA [171]. Increased locomotion in rodents after MDMA may regulated in part by 5HT2C and 5HT2B receptors, possibly through indirectly regulating dopamine and serotonin release [134, 172], and at least one study reported that blocking alpha1 adrenergic receptors reduced locomotor activity after 5 mg/kg MDMA [171]. In contrast, rhesus monkeys do not exhibit increased locomotor activity after receiving up to 2.4 mg/kg MDMA [173].

Behavioral Effects

Several dose-dependent differences on behavioral tests in rats given MDMA have been reported, including increased anxiety-related behaviors thought to be associated with serotonin syndrome [174], and decreased social anxiety at 5 mg/kg i.p. [141]. Rats given 7.5 mg/kg MDMA, equivalent to four times the dose tested in humans, exhibited increased anxiety in the elevated plus maze [175], while rats given 15 mg/kg MDMA, equivalent to eight times the dose tested in humans, exhibited reduced anxiety on the maze. A study in mice reported that doses from 0.5 to 20 mg/kg produced anxiogenic responses on the plus maze [176]. A study of the sub-acute effects of four different doses of MDMA given daily for 1 week, found reduced anxiety with 1.25 and 2.5 mg/kg and increased anxiety with 5 and 10 mg/kg [165]. Lower doses used in these studies are comparable to dose used in human research and nonmedical settings. However, sample sizes used in the study were small. Rats given higher doses also reduced aggressive behavior as well as social investigation. Mice placed in the forced-swim test, an animal model of antidepressant action, exhibited less immobility after acute doses of 2.5, 5, and 10 mg/kg MDMA, considered an indicator of antidepressant activity [176]. However, as previously noted, MDMA can increase locomotor activity.

Some researchers have proposed that behavioral tests of anxiety may instead be measuring risk-taking behavior, or impulsivity [177]. The possibility of gender-specific effects cannot be ruled out, given the high prevalence of all-male samples [178, 179]. Preclinical data in animals suggests that the profile of neurotransmitter release observed after MDMA administration may increase the risk of mania in some individuals [180], although mania has not been a reported as a side effect of MDMA or Ecstasy in humans. Conflicting findings on anxiogenic and anxiolytic dose-dependent effects of MDMA are likely to have limited applicability to humans.

A behavioral study measuring the effect of a single dose of 10 mg/kg in mice following social defeat detected additive effects on measures of memory, anxiety, and depression, 1

to 10 days after drug administration. Social defeat and MDMA both affected passive avoidance and object recognition memory, and the combination of the two produced greater memory impairment. Social defeat and MDMA also increased immobility in the tail suspension test, and increased motion and increased tendency to remain in the center of the open field, [181]. Administering an additional 5 mg/kg MDMA in the open field resulted in slower speed in mice that underwent social defeat and received MDMA. Social defeat lowered body temperature, however, when immediately followed by MDMA, body temperature increased and blood cortisol decreased, and the authors refer to this as evidence for stress enhancing impaired cognition and depression-like behavior after MDMA. However, they did not employ a test of direct effects of corticosterone, and it is possible that social defeat and MDMA could produce independent effects.

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 [141]. Subsequent studies 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 via serotonin release [140, 182, 183]. 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 [86, 184-186]. 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 [23, 187-189]. Pitts and colleagues reported observing greater prosocial effects of MDMA when compared with the psychostimulant methamphetamine in squirrel monkeys [190], confirming rodent findings in primates. The effects were seen with racemic MDMA and with each enantiomer, and they were dampened by administration of a 5HT2A receptor antagonist. MDMA appears to have prosocial effects on animals less closely related to humans, including octopuses and zebrafish [191, 192]. The study in octopuses examined the octopus serotonin transporter gene, determining that the receptor that binds MDMA is conserved across species.

Coordination

The effects of MDMA administration on coordination has been tested in primates and rodents. Rhesus monkey coordination was tested in a 4-day repeated dose regimen, receiving a high dose of 10 mg/kg [193]. It was found that MDMA acutely disrupted bimanual motor coordination in rhesus monkeys following MDMA administration. These effects on bimanual motor coordination were apparent for a week following high dose MDMA administration and returned to baseline at the 1 week mark [193].

The effects of MDMA on fine-motor coordination of baboons has been studied in a single arm, single-dose (0.32 to 7.8 mg/kg, spaced 5 days apart) study [194]. Fine-motor incoordination was not observed in the fine-motor task, but rather a dose-dependent delay in initiating the task was observed. It should be noted that 6 months prior to this study, the baboons in question had been used extensively for toxicology studies of both GABA-A allosteric modulators (chronic administration) as well as self-administration of cocaine, ethanol, and five distinct sedative compounds [195]. These confounding factors could

potentially reduce the validity of the results as it was undocumented whether they resulted in any chronic effects, such as dopaminergic disruption.

Coordination was also ascertained in mice in a repeated dosing regimen using both a neurotoxic and non-neurotoxic dose (twice daily, 3 or 30 mg/kg for 4 days) [196]. The effects of MDMA administration on coordination in the mouse was measured using the road test. The mice were tested 24 hours and 48 hours post MDMA administration. Unlike the rhesus monkeys, mice showed no apparent disruption of motor coordination following MDMA administration [196].

Sensorimotor Reflex Responses

The effects of 20 mg/kg MDMA on the startle reflex in rats has been tested in a 10-day repeated dosing study [197]. It was observed that MDMA acutely affects the baseline magnitude of the acoustic startle response, while having no long-term effects on the startle response. It was furthermore found that pre-pulse inhibition (unlearned suppression of the startle response) was profoundly reduced in rats exposed to MDMA, both acutely and long-term [197].

In order to evaluate MDMA's effects on bruxism, specifically jaw-clenching, the effects of MDMA on the jaw-opening reflex was tested in rats, both in a single and repeated dose regimen (20 mg/kg once or same dose, twice daily for 4 days) [198]. It was found that single-dose administrations of MDMA exerted an inhibitory effect on the jaw-opening reflex. For repeated administrations this effect was amplified and found to be mediated by enhanced noradrenergic inhibitory mechanisms that are responsible for regulating the jaw-opening reflex [198].

Body Temperature

Rodents have generally been used to study the hyperthermic effects of MDMA. Rodents have a much smaller body mass and do not perspire but use their tail to regulate body temperature, which has a large surface to volume ratio, and is perfused with many blood vessels for thermoregulation. Since thermoregulation is different in rodents and humans [199], findings may have limited applicability to humans. MDMA doses that are moderate to high elevate body temperature and disrupt thermoregulation in mice [98], and doses of MDMA in the 1 to 2 mg/kg range only cause a slight increase in body temperature [200]. Rats given doses of 10 mg/kg MDMA (s.c. and i.p.), but not 2 mg/kg, experienced increases in body temperature correlated with levels of the active metabolite MDA [77, 201]. A study of rats receiving subcutaneous injections of 1 and 3 mg/kg MDMA demonstrated minimal effect on brain hyperthermia using thermal couplers installed in the nucleus accumbens, and in another study, in the striatum [202], however ambient temperatures of 29°C and social interaction during group housing had a potentiating effect on malignant hyperthermia at 9 mg/kg (s.c.) [203]. MDMA effects on body temperature are susceptible to changes in ambient temperature in rodents, with high ambient temperature significantly increasing body temperature in mice and rats, and low ambient temperatures reducing it [155, 204, 205]. A study in rats found that age affects degree of body temperature elevation after 2x5 mg/kg MDMA, with 20-month old (aged) rats exhibiting significantly higher body temperature than young (40 days old) rats [206].

The aged rats in this study also exhibited more signs of brain and liver toxicity than younger rats. It is currently unknown whether MDMA-related increase in body temperature occurs in older humans. The MDMA-induced impairment in thermoregulation is caused, at least in part, by peripheral vasoconstriction in the tail, an effect mediated by brain neurotransmitter activity [207, 208].

High doses of MDMA also produce significant elevations in body temperature in primates [93, 209, 210]. At doses closer to those humans ingest [211], monkeys exhibit only slight to moderate elevation in body temperature [173, 212]. In contrast to findings in rodents, primates, including humans, are not susceptible to changes in ambient temperature when given MDMA, exhibiting slight to moderate increases in body temperature regardless of the temperature of the environment [173, 211, 212], 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 after MDMA administered in cool temperatures and higher body temperatures in another group given MDMA at warm temperatures [213]. Findings in rodents do not extrapolate well to primates in this area. Given that the thermoregulatory effects in rodents are highly dose-dependent, most physiological effects seen after low to moderate MDMA administration suggest that a controlled environment and moderate doses would be sufficient to mediate physiological complications associated with hyperthermia, including cardiovascular, osmoregulatory, neurological, and immunological effects.

4.1.3.2 Cardiovascular System

The sponsor has completed an appropriately controlled, in vitro IKr Assay (commonly referred to as a human Ether-à-go-go-Related Gene (hERG) assay) per ICH S7A and S7B. Final results from the cell patch clamp measure found an IC50 of 206 µM and a Hill coefficient of 1.1 for MDMA at near-physiologic temperature (33°C), with a 170-fold ratio over the expected unbound MDMA plasma concentration in clinical exposure at 2 mg/kg p.o. [214]. These results demonstrate that MDMA has minimal risk of QTc prolongation or *Torsade de Pointes* (TdP), which is one of the most critical types of arrhythmia associated with sudden death. In comparison, SSRIs are known to carry low to moderate risk of QTc prolongation, including available PTSD medications paroxetine and sertraline [215, 216].

In vivo assessments of cardiovascular effects of MDMA in animals detected increased sympathomimetic activity, as seen in humans [98, 149]. An injection of 2 mg/kg MDMA elevated heart rate in rabbits [148]. Ten mg/kg MDMA produced a relatively larger increase in heart rate in rats than in blood pressure, an effect possibly controlled by beta adrenergic receptors [149]. The researchers found that MDMA has both pressor and depressor effects, acting through adrenergic receptors [217-219]. Another study in rodents also suggests that norepinephrine may play a role in cardiovascular effects [220], findings that have been more intensively investigated in humans [221-224]. Given the affinity of MDMA for the NET, it is possible that the cardiovascular effects of MDMA could be partially attributed to norepinephrine signaling in the peripheral nervous system.

Injections of 20 mg/kg MDMA in conscious rats assessed by radio telemetry (10.7 times the equivalent dose in humans) found that MDMA caused a prolonged increase in blood

pressure [218]. In the same study, MDMA was found to produce mild isotonic contractions of aorta and vas deferens vascular tissue in anesthetized rats, but could also inhibit prejunctional contractions evoked by stimulation [218]. In-vitro work in human internal mammary artery suggests that contractile effects may increase at high temperatures (40°C versus 37°C) and that some metabolites may contribute to this effect [225].

4.1.3.3 Respiratory System

A combination of known pharmacodynamics of MDMA provide justification for not conducting toxicology studies of the IMP on the respiratory system. Animal studies show that serotonin agonism increases respiratory drive via actions at 5HT1A, 5HT7, and 5HT4A. In humans, 5HT1A agonist buspirone and the 5HT4A agonist mosapride did not increase nor decrease respiratory drive [226]. MDMA causes serotonin reuptake inhibition and carrier-mediated release of serotonin which causes indirect agonism of serotonin receptors and has known sympathomimetic effects. MDMA does not have detectable affinity for the mu opioid receptor. In addition, two peer-reviewed scientific publications of clinical studies with MDMA found there were no significant effects on body temperature measured at tympanic membrane, respiratory rate, or blood oxygen saturation by pulse oximetry [17, 211].

4.1.3.4 Hepatic System

MDMA is primarily processed through the hepatic route, with 50 to 75% being metabolized. Standard toxicity studies EMD-SC-001 and EMD-SC-002 failed to find liver damage after MDMA administration in rats or dogs after 28 days of daily exposure [95]. In a sponsor-supported pilot dose range finding study of Sprague-Dawley rats (EMD-AT-001), oral toxicity was assessed in a 13-day increasing dose regimen [227] from 25 mg/kg to 300 mg/kg. This study found significant elevations of the liver toxicity markers alanine aminotransferase (ALT) and aspartate transaminase (AST) in male rats. Despite a rise in these markers, gross pathology and microscopy of liver tissue failed to show any liver damage [227].

4.1.3.5 Renal System

Renal clearance of MDMA is between 8% to 11% of the parent compound. All metabolites of MDMA in urine were detected as glucuronide and sulfate conjugates. Acute symptomatic hyponatremia is associated with the syndrome of inappropriate antidiuretic-hormone secretion (SIADH) involving raised antidiuretic-hormone, also known as AVP [228]. SIADH refers to disorders related to water and sodium balance characterized by the impairment of urinary dilution and hypotonic hyponatremia in the absence of renal disease or other identifiable non-osmotic stimuli known to activate the release of AVP [229]. MDMA is known to cause central release of both oxytocin and AVP through indirect effects of serotonergic signaling as previously described, and this activity indicates that it is not accurate to attribute the osmoregulatory effects of Ecstasy to SIADH, but rather this should be characterized as a pharmacological effect on AVP secretion. AVP plays a key role in osmoregulation and is released upon a change in plasma osmolality [230]. AVP is also involved in the response and adaptation to stress,

through its effects on the HPA axis [230]. The rise in AVP does not seem to be part of a generalized stress response, but results from a pharmacological effect compounded by excessive fluid ingestion [231].

AVP is a key regulator of water balance in the body, and has antidiuretic actions when acting at its V2 receptor subtype in the kidneys [232, 233]. In 28-day repeated dose studies, the only renal change observed microscopically was mild to minimal hydronephrosis, which the researchers attributed to treatment-related polyuria (abnormally large urine production). Gross pathology revealed enlarged urinary bladders (most likely polyuria-related) in some animals and were deemed potentially treatment-related. MDMA can influence water regulation by activation of the AVP system, as shown in several animal studies. A study of isolated in vitro rat hypothalamus initially reported AVP and oxytocin release after MDMA and its metabolite HMMA [150]. In vivo drug-discrimination studies in rats suggest that AVP receptors are involved in producing interoceptive effects of MDMA [142]. When 10 mg/kg i.p. MDMA was administered at 30°C ambient temperature to male Wistar rats, MDMA induced expression of Fos, a marker of neural activation, in the supraoptic nucleus, a brain region important for osmoregulation and a key mediator of oxytocin and AVP release [234]. This finding suggests that MDMA can affect the renal system in rats at high doses administered at warm ambient temperatures. However, due to<20% renal clearance of the parent compound, a renal impairment study is not planned.

4.1.4 Pharmacodynamic Drug Interactions

MDMA has been shown to interact with numerous CNS active compounds in animals, with effects on behavior, neurotransmitters, gene expression, and thermal regulation among others. When given with moclobemide, a reversible inhibitor of monoamine oxidase A, 10 mg/kg (i.p.) MDMA has been shown to cause statistically significant increases in 5-HT outflow and body temperature in rats [235]. Caffeine has also been shown to increase MDMA associated hyperthymia in rats when given at 10 mg/kg with 2.5 mg/kg of MDMA. Increased hippocampal 5-HT loss was also seen in the caffeine treated animals, which the authors stipulate may result in increased MDMA toxicity [236].

Although previous statements have highlighted deleterious pharmacodynamic drug interactions of MDMA with other CNS active agents, potential for increased efficacy is also possible with concomitant administration with these agents. MDMA efficacy for depression (in a mouse forced swimming test model) has been shown to be synergistic with non-effective doses of mephedrone, a synthetic amphetamine derivative [176].

Some CNS active agents have been shown to decrease MDMA adverse effects in animals. Both mirtazapine, a direct serotonin antagonist, and fluoxetine, a selective serotonin reuptake inhibitor, have been shown to reduce MDMA related hyperthermia in rats [237]. Interesting both mechanisms, serotonin blockade and serotonin reuptake inhibition, were shown to have this effect. Other authors have shown that chronic fluoxetine treatment partly attenuates the long-term anxiety and depressive symptoms induced by MDMA in rats [238]. Note that the pharmacodynamic interaction of MDMA with fluoxetine is complicated by also being accompanied by a pharmacokinetic

interaction, as both drugs are substrates and inhibitors of CYP2D6 [239]. Although these effects seem positive, they need be balanced by the possibility of lower efficacy for the primary indication of PTSD when given concurrently.

4.2 Pharmacokinetics and Product Metabolism in Animals

For context, it is important to note that MDMA clinical pharmacology differs from many other drugs in psychiatry in that it does not require reaching of steady state for onset of effect like Selective Serotonin and Norepinephrine Uptake Inhibitors (SSRIs), SNRIs and other common drugs. In clinical trials MDMA is given in single-dose sessions consisting of an initial dose followed by a supplemental dose administered 2 hours later, followed by abrupt discontinuation. MDMA's pharmacology is complicated by non-linear pharmacokinetics, which has been observed in multiple mammalian models. Due to the nonlinear characteristics of MDMA, bioavailability is likely incomplete and variable across doses (see Section 4.2.1 Absorption). MDMA has been shown to be primary eliminated by hepatic metabolism with minimal renal contribution in animals (see Section 4.2.3 Metabolism and 4.2.4 Elimination). MDMA has also been shown to have pharmacokinetic drug interactions with many drugs used in psychiatry, as both the perpetrator and victim compound due to its metabolism though and autoinhibition of CYP2D6 (in humans), a common metabolizing enzyme of many CNS agents (see Section 4.2.5 Pharmacokinetic Drug Interactions). Additionally, MDMA has been shown in nonclinical studies to have a large volume of distribution and high CNS penetration (see Section 4.2.2 Distribution). A summary of the pharmacokinetics of MDMA across multiple mammalian species is available in Table 2.

4.2.1 Absorption

At doses of 2 mg/kg, MDMA is rapidly absorbed by rats by both oral and subcutaneous routs administration, with an observed Tmax of 0.56±0.31 hours by the oral route. At higher oral doses of 10 mg/kg a slightly shorter Tmax 0.31±0.13 hours was observed in rats [77]. Although no robust IV MDMA data is available to the sponsor at the time of writing this edition of the IB, Baumann and collogues measured IP exposure of MDMA in rats in their 2009 article. At 2 mg/kg the p.o. to i.p. ratio of MDMA AUC can be calculated to be 0.37. This calculated relative bioavailability of 37% can be thought to approximate the absolute bioavailability of MDMA in rats. Note that at doses of 10 mg/kg in rats, the p.o. to i.p. relative bioavailability increases to 65%. At low doses, gender effects on exposure have been observed in rats. This effect dissipated at 5 mg/kg and is not expected nor observed in higher mammals or humans [151].

In squirrel monkeys, Mueller and colleagues observed an oral Tmax of 1 hour at 1.4 mg/kg and as long as 1.3 hours at 10 mg/kg [240]. At doses of 7.4 mg/kg p.o. to i.p. relative bioavailability can be calculated of 68% [93]. Mechan and colleagues also observed increased exposure to MDMA upon repeated dosing, further illustrating MDMA's nonlinear pharmacokinetic characteristics. A 2011 article from Mueller and colleagues observed a prolonged Tmax of 7.1 hours at 5 mg/kg in baboons, a result not seen in other non-human primates [241].

Additionally, see Table 2 for a list of exposures across multiple mammalian species.

4.2.2 Distribution

MDMA has been shown to be partially bound to plasma proteins in mammals. The mean unbound fraction of MDMA in plasma was measured in rabbits by De Letter and colleges to be 63%±3 (n=6) at a concentration of 400 ng/ml [242]. In vitro plasma-protein binding of MDMA in mice is lower than in rat and human serum, in which it is approximately equal [243]. This indicates that the same dose of MDMA in mice will have more active drug available in serum than in rats and humans. Mice were shown to have lower plasma protein binding in vitro compared to rats and humans, and only mice exhibited stereoselective plasma protein binding [243].

The volume of distribution of MDMA at 1 mg/kg was observed to be 7.41 to 7.52 L/kg in rats [151]. From Baumann and colleagues' published noncompartmental data, the volume of distribution is 4.43 to 9.52 L/kg in rats.

Work from De Letter and colleagues has identified a 2-compartment model of MDMA pharmacokinetics in rabbits. The total volume of distribution at steady state was reported to be 4.9 L/kg. A central compartment of 1.9 L/kg was elucidated by the model, suggesting a large peripheral compartment in rabbits, leading to a biexponential half-life (alpha-t1/2 of 5 minutes and a beta-t1/2 of 63.5 minutes). The authors also observed some accumulation of MDMA in the vitreous fluid of rabbits [242].

MDMA has been shown to have high distribution into the CNS compartment. Scheidweiler and colleagues observed a significantly higher AUC of MDMA in the striatum of mice across doses from 10 mg/kg to 40 mg/kg. Striatum to plasma ratios were observed from 6.5 to 12.4, illustrating MDMA's high CNS penetration [244].

Additionally, MDMA has been shown to distribute into amniotic fluid and the fetal brain in pregnant rats after a single 15 mg/kg SC injection. Although amniotic drug exposure was shown to be lower than in maternal plasma, fetal brain MDMA and MDA exposure was shown to be much higher than that observed in maternal plasma [245]. The volume of distribution of neonatal rats is comparable to adult rats and has been reported to be 4.61 to 4.83 L/kg [246].

4.2.3 Metabolism

MDMA is metabolized via two hepatic pathways in rodents (see Figure 2 for a comparison to human metabolism). In the major pathway in rats, MDMA is O-demethylated by cytochrome P450 CYP2D1 and 3A2 to form HHMA, which is O-methylated to generate HMMA by catechol-O-methyltransferase (COMT). In the minor pathway in rats, MDMA is N-demethylated by CYP1A2 and 2D1 to form MDA, which is an active metabolite. MDA is O-demethylated by the same enzymes as MDMA, with subsequent metabolism by COMT. Metabolites of MDMA are excreted in urine as glucuronide and sulfate conjugates. MDMA and metabolites have shorter half-lives in rats than humans at comparable doses based on plasma C_{max} values. Rats tend to form more MDA and glucuronide-conjugated metabolites than humans [247]. As MDMA dose increases above 2.5 mg/kg subcutaneous (s.c.) or intraperitoneal (i.p.) in rats, a larger

percentage of the administered dose is shunted to the N-demethylation pathway, resulting in greatly enhanced formation of MDA [201]. Comparison of metabolic pathways between rats and mice given 10 mg/kg i.p. MDMA indicate that 49.1% of MDMA is metabolized through the HMMA pathway in mice versus 72% in rats, and 18.3% of MDMA is metabolized through the MDA pathway in mice versus 28% in rats based on AUC ratios to MDMA. MDMA at 10 mg/kg was also found to be eliminated more rapidly in mice (0.4 hours, i.p.) than rats at (1.1 hours, s.c.) [77, 244].

To address questions of the applicability of interspecies scaling models and nonlinear pharmacology of MDMA, a study examining MDMA and metabolites in rats given 2.5, 5, and, 10 mg/kg s.c. found that MDMA metabolism is nonlinear in rats, with 2.5 mg/kg producing plasma C_{max} levels approximating those seen in humans receiving between 75 and 100 mg [24, 201, 248]. Injections of 2 mg/kg s.c. or i.p. in rats were found to be similar to oral administration of 100 mg MDMA in humans based on plasma MDMA and metabolite concentrations [77]. Based on plasma values, a dose of 3 mg/kg i.p. MDMA administered in mice was comparable to a single oral dose of 100 mg in humans [249]. Studies in rats and mice provide compelling evidence of nonlinear pharmacokinetics, likely due to saturation of metabolic enzymes, determined by greater than expected AUC values for MDMA and MDA after subsequent MDMA doses, while AUCs for HHMA and HMMA remained lower than expected [201, 244]. For example, when comparing the AUCs of the 2 mg/kg SC data to the 10 mg/kg SC from Bauman [77] and Concheiro [201] respectively, the AUC observed at 10 mg/kg is 1.89x higher than expected from the 2 mg/kg study. This is consistent with nonlinear pharmacokinetics observed in humans (described later in Section 6.2.1 Pharmacokinetics and Product Metabolism in Humans) and is likely due to autoinhibition of the CYP450 system.

MDMA exposure, half-life, and other parameters are summarized below in Table 2 for rats, mice, squirrel monkeys, and humans.

Table 2: Pharmacokinetic Constants for Plasma MDMA After Various Routes of Administration to Humans or Animals

	C_{max} (ng/ml)	AUC (h•ng/ml)	T_{max} (h)	$t_{1/2}$ (h)	References
Rat [A]					
2 mg/kg i.p.	210±108	163±56	0.14±0.08	0.80±0.16	[77]
2 mg/kg s.c.	196±50	304±65	0.75±0.29	0.79±0.14	[77]
2 mg/kg p.o.	46±15	61±42	0.56±0.31	0.77±0.11	[77]
10 mg/kg i.p.	2257±131	3432±278	0.13 ±0.04	1.08±0.14	[77]
10 mg/kg s.c.	1130±138	3146 ±514	1.10±0.22	1.27±0.39	[77]
10 mg/kg p.o.	966±49	2226±301	0.31±0.13	1.62±0.41	[77]
2.5 mg/kg s.c.	164.1±47.1	272.1±71.6	0.6±0.2	1.1±0.9	[201]
5 mg/kg s.c.	370.8±41	879.1±133.2	0.9±0.6	0.9±0.1	[201]
10 mg/kg s.c.	893.9±90.7	2879.9±491.5	1.1±0.4	2±0.6	[201]
Mouse [B]					
3 mg/kg i.p.[C]	369.8	---	0.17	0.6	[249]
10 mg/kg i.p.	1109±87	1233±53	≤0.3	0.4	[244]
20 mg/kg i.p.	2152±82	2611±86	≤0.3	0.6	[244]
Squirrel Monkey					
1.4 mg/kg p.o.	100.2±51.5	340.3±248.4	1±0.4	1.8±0.9	[240]
2.8 mg/kg p.o.	312.7±92.8	1314.2±581.5	1.1±0.4	2.1±0.8	[240]
5.7 mg/kg p.o.	723.6±228	3866.2±891	1.3±0.9	2.6±0.7	[240]
10 mg/kg p.o.	1594.5±295.6	12,839.2±2144.6	1.3±0.9	4.2±1.5	[240]
7.4 mg/kg s.c.	1227±167	5006±528	---	3.5±0.9	[93]
7.4 mg/kg p.o.	773±157	3408±821	---	3.1±0.5	[93]
Human					
1.0 mg/kg p.o.	147±10	1389±119	2.3±0.2	7.2±0.6	[241]
1.6 mg/kg p.o.	292±76	3485±760	2.4±0.6	8.1±2.1	[248]
1.6 mg/kg p.o.	254.7±60.4	3070.6±673.4	2.4±0.6	8.4±1.6	[250]
2.0 mg/kg p.o.	442-487	5133-5232	1.5-2.0	6.9-7.2	[24]

4.2.4 Elimination

Although hepatic metabolism is thought to be the major route of elimination across mammalian species, MDMA and its metabolites have been shown to be present in urine of rats for as long as 48 hours after a single 20 mg/kg MDMA dose [251]. Additionally, De Letter and collogues have shown that at intravenous doses of 1 mg/kg only 6% of the MDMA dose given rabbits was found unchanged in urine [242].

In contrast to most small molecule drugs, MDMA has been shown to have rapid clearance on the first day of life of rats treated with 20 mg/kg of MDMA. Peculiarly, MDMA clearance has been observed to rapidly decrease from 1.26 L/h/kg to 0.81 L/h/kg by day 11 of life in rats [246].

To date, there is no known well controlled animal study quantifying excretion of MDMA into breastmilk.

4.2.5 Pharmacokinetic Drug Interactions

MDMA has been shown to effect the absorption, distribution, and metabolism of tramadol in rats, leading to decreased in half life and an increases in exposure at relatively low MDMA doses 0.5 mg/kg [252]. The data from this study suggests that the

interaction involved both CYP2D6 and CYP3A4 specificity. MDMA has also been shown to interact with methamphetamine in rats, leading to increased exposure to both MDMA and methamphetamine with concurrent exposure [253]. The authors of the study warn that interactions with other amphetamine derivatives and CYP2D6 substrates are likely.

MDMA is also likely to interact with many approved psychiatric drugs. Upreti and Eddington described the complicated interaction of MDMA with fluoxetine in rats [239, 254]. The authors showed that pretreatment of rats with fluoxetine resulted in an increase in MDMA (1.4-fold) and MDA (1.5-fold) exposure in both brain and plasma. Additionally, the elimination half-life was increased for MDMA (2.4 vs. 4.9 h) and MDA (1.8 vs. 8.2 h) with fluoxetine pretreatment. As MDMA and fluoxetine are both substrates and inhibitors, and interact with (or metabolized by) the same enzyme, CYP2D6, this profound increase in MDMA exposure was too be expected. The authors also partially ruled out P-glycoprotein as a potential site of drug-drug interactions with MDMA ([239]. It is likely that other CYP2D6 substrates or inhibitors used in psychiatry (such as duloxetine, amitriptyline, doxepin, fluvoxamine, paroxetine, or trazadone) may interact with MDMA in small mammals.

4.3 Toxicology

MDMA has been studied in single-dose (see Section 4.3.1 Single-Dose Toxicology Studies) and repeat-dose toxicology studies (see Section 4.3.2 Repeat-Dose Toxicology Studies). The sponsor has also completed in vitro and in vivo safety studies addressing genotoxicity (see Section 4.3.3 Genotoxicity), fertility and early embryonic development (see Section 4.3.6.1 Immunological Effects), and embryo-fetal development with toxicokinetic analyses (see Section 4.3.6.2 Mechanistic Effects). Independent nonclinical studies support that MDMA possesses abuse potential, but much less than structurally related compounds, such as amphetamine (see Section 4.3.6.3 Abuse Potential). Overall, sponsor conducted studies have shown MDMA was well tolerated with no mortality or significant toxicologic findings after p.o. administration to rats (<150 mg/kg) and dogs (<9 mg/kg). Several more sponsor-initiated safety studies are in progress and are listed in Table 1.

4.3.1 Single-Dose Toxicology Studies

In a sponsor-supported single-dose study of Sprague-Dawley rats (EMD-AT-001), 10 rats per gender were exposed to 300 mg/kg. Of these, 40% per gender died, and 12 survivors were sacrificed 3 days later [227]. The single-dose oral LD50 was estimated at 322 mg/kg, which is 6x higher than the LD50 for i.p. injection. These findings show that MDMA administered orally at 300 mg/kg (approximately 100 to 150x the accepted human therapeutic dose), resulted in marked adverse clinical reactions, including death; with physiological and morphological changes in the kidney (hydronephosis), and possible testicular tubular changes. No evidence of histologic brain damage was found in the survivors using cresyl violet, luxol fast blue, and Bodian's silver stain in standard histopathology assessments.

Single doses between 5 and 60 mg/kg have been administered in rodents. Single doses in this range have transient effects on serotonin depletion [77, 201, 250], likely due to reversible inhibition of tryptophan hydroxylase [255-257], which prevents additional serotonin from being produced and released. A study of the long-term effects of a single dose of 5.7 mg/kg MDMA on estimated SERT sites in the brains of squirrel monkeys reported reduced SERT sites in some frontal, temporal and parietal areas [258]. The plasma C_{max} of 725 µg/L in squirrel monkeys was 3x greater than what is observed in humans after a single dose of 100 mg MDMA [247, 259, 260].

4.3.2 Repeat-Dose Toxicology Studies

In order to establish the Clinical Development Program for MDMA, 28-day repeat-dose general toxicity studies were conducted in both genders of Sprague-Dawley rats (53 male, 52 female) (MDMA 0, 10, 50, 100 mg/kg oral gavage) and the dog (12 male, 12 female) (MDMA 0, 3, 9, 15 mg/kg oral dosing with gelatin capsules) [95]. The initial highest dose was set at 18 mg/kg but after the death of one female dog, the highest dose was subsequently reduced to 15 mg/kg. Dosing was once daily for 28 days. This research was performed within the U.S., which is a member of the Mutual Acceptance of Data (MAD) program, and studies were conducted in compliance with GLP in the USA based on standards in 1986 to the satisfaction of FDA. Both sexes of dogs administered 9 and 15 mg/kg of MDMA and rats receiving 50 and 100 mg/kg gained less weight than controls and the 3 mg/kg group, with significant differences in food consumption observed as early as the first week which were no longer significantly different by the third week for the rats and the fourth week for the dogs. Gross observations at necropsy in the dog possibly related to MDMA included reduced testicular size for one of three dogs receiving 9 mg/kg and one of three dogs receiving 15 mg/kg and prostatic enlargement in two dogs receiving 15 mg/kg. No gross lesions were seen in the rats at necropsy. Blood chemistry and urinalysis values were unremarkable in the dog. Clinical pathology findings showing a trend to decrease with dose in the rat were urinary pH, blood urea nitrogen, glucose, creatinine (females), lactate dehydrogenase (females), and chloride, in contrast total white blood cell count (WBC) and phosphorus showed a trend to increase with dose. No MDMA-related lesions were seen in the brains of either species. Histopathological examinations showed mild, diffuse atrophy in the two dogs with reduced testicular size. Mild, focal atrophy was furthermore observed in the testes of one additional dog from the 15 mg/kg group. The two dogs with grossly enlarged prostates showed hyperplasia of the prostate. Brain lesions attributable to MDMA were observed in 5 of 10 male rats administered 100 mg/kg (no lesions were observed in females). These lesions presented as vacuolated lesions apparent in the fiber tracts of the brainstem adjacent to the trigeminal nuclei. Possibly MDMA-related lesions were observed in the CNS of the dogs as well. In the cerebrum, these lesions included floccular changes of white matter, focal neural malacia and focal cellular infiltrates. Neural chromatolysis was observed in the brainstem. However, the authors noted that it is difficult to extrapolate the findings due to the low sample size (three dogs per gender per group).

In a MAPS-sponsored pilot dose range finding study of Sprague-Dawley rats (EMD-AT-001), oral toxicity was assessed in a 13-day increasing dose regimen [227]. The initial dose started at 25 mg/kg and was increased by 25 mg/kg on a daily basis until 300 mg/kg

was reached. Adverse reactions were observed in all doses above 25 mg/kg and included hyperexcitability, uncontrolled urination, piloerection and bulging eyes. Tremors, muscle spasms, impaired movement, convulsions and death were observed in the highest of dose levels, in the range of 150 and 300 mg/kg. Blood chemistry analyses suggested possible liver and kidney damage in animals receiving higher doses, however, gross pathology and microscopy found no treatment-related damage to the liver. The only renal change observed via microscope was mild to minimal hydronephrosis, which the researchers attributed to treatment-related polyuria (abnormally large urine production). Minimal tubular atrophy was seen in the testes of 3 of the 20 treated male rats, suggesting a possible relationship between high dose, repeated MDMA treatment and minimal testicular atrophy in the male rat. Gross pathology revealed reddened lungs and enlarged urinary bladders (most likely polyuria-related) in some animals and were deemed potentially treatment-related. Histopathological observations of brain tissue revealed no signs of brain damage in any of the treated rats.

4.3.3 Genotoxicity

A sponsor funded in vitro bacterial reverse mutation Ames assay was conducted for MDMA by Charles River Labs. This GLP compliant study was completed April 2020. Four tester strains of Salmonella typhimurium (TA1537, TA98, TA100, and TA1535) and one Escherichia coli strain (WP2 uvrA) were used for mutagenicity testing. After a range finding assay, MDMA HCl was tested at 100, 250, 500, 1000, 2500, and 5000 µg/plate using the plate incorporation method. Precipitates and cytotoxicity were not observed in any strain with or without metabolic activation. Additionally, criteria for a negative response (via Ames assay) were met for all tested strains with and without metabolic activation. These data support the conclusion that MDMA is negative for mutagenic activity in Salmonella typhimurium and Escherichia coli.

A sponsor funded in vitro genotoxicity chromosome aberration test in Chinese hamster ovary (CHO) cells was conducted for MDMA by Charles River Labs. This GLP compliant study was completed April 2020. Chinese hamster ovary cells cultures were treated with MDMA, positive control, or vehicle control in the presence and absence of an Aroclor™ 1254-induced rat liver S9 microsomal fraction (for metabolic activation). After a range finding assay, MDMA was tested at range of 60 to 240 µg/mL. No statistically significant test article-related increases were observed in the mean percent of cells with aberrations. Additionally, no statistically significant increases in polyploidy or endoreduplication were observed. MDMA was considered negative for inducing structural aberrations in Chinese hamster ovary cells with and without metabolic activation under the conditions of this test system. These data support the conclusion that MDMA is negative for genotoxic activity in CHO cells in the presence and absence of metabolic activation.

A sponsor funded GLP-compliant in vivo genotoxicity micronucleus study was conducted for MDMA in male Sprague Dawley rats in April 2020. The vehicle control (Nanopure Diamond ultrapure water) or the maximum tolerated dose of 100 mg/kg MDMA were administered orally via gavage once daily for 2 consecutive days. Bone marrow was harvested approximately 24 hours after the last dose was administered for the vehicle and test article groups. The positive control (cyclophosphamide; stock slides

prepared in WIL-99737) was administered orally via gavage and harvested approximately 24 hours after dose was administered. MDMA did not produce statistically significant or dose-dependent increases in the %MN-PCEs in male rats at any dose level as compared to the vehicle control. No bone marrow cytotoxicity (decreases in PCE:TE ratio) was noted in any male rats at any 3,4-methylenedioxymethamphetamine hydrochloride dose level. Group mean values for %MN-PCEs and PCE:TE ratios for the vehicle and positive controls were within 95% historical control intervals obtained by Charles River Skokie, demonstrating the acceptability of the assay with the following exception. The %MN-PCEs for the positive control male rats (2.91) produced a higher response when compared to the 95% historical control interval (0.13 to 2.59). This demonstrated a more robust positive response. Therefore, MDMA was negative for clastogenic activity and/or disruption of the mitotic apparatus under the conditions of this assay.

4.3.4 Carcinogenicity

Based on negative genotoxicity studies, there is no cause for concern of carcinogenic risk of MDMA and carcinogenicity studies have been waived by regulatory agencies. No tumors were reported after daily 28-day repeated dose toxicology studies of MDMA in rats or dogs described in Section 4.3.3 Genotoxicity.

4.3.5 Reproductive and Developmental Toxicity

Preliminary teratological studies in rats (N=12 per dose) given 0, 2.5, or 10 mg/kg MDMA by gavage on alternate gestational days (GD) 6 to 18 found no abnormalities in gestational duration, litter size, neonatal birth weights, or birth defects (N=10 litters per dose), despite statistically significant reduction in maternal weight gain at 10 mg/kg [261]. These results are in contrast to physiological abnormalities resulting from prenatal methamphetamine and d-amphetamine exposure in mice and rabbits [262]. In a single-generation fertility and developmental toxicity study, C57BL/6 mice (N=25 per dose per gender) received a daily dose of 0, 1.25, 5, or 20 mg/kg/day MDMA via gavage [263]. This suggested that MDMA could have weak reproductive toxicity at high doses in mice, when MDMA exposure starts 2 weeks prior to mating and continues through GD15, which temporally covers ovulation through organogenesis and closure of the hard palate in the females and spermatogenesis in the males. In a separate perinatal/postnatal toxicity study, C57BL/6 female mice (N=25) received a daily dose of 0, 1.25, 5, or 20 mg/kg/day MDMA via gavage from GD6 slightly after implantation through postnatal day (PND) 21 end of lactation [263]. When MDMA was given to only the females from GD6 to the end of lactation, there were no signs of impaired development and no significant differences in sexual development or reproductive capacity of F1 and F2 mice.

The sponsor has completed a definitive study of the effects of MDMA on Fertility and Early Embryonic Development to Implantation in both genders of rats. In this study, males were dosed once daily for 28 days prior to pairing and continued to euthanasia. Females were dosed 21 days prior to pairing and continued through GD 7. The copulatory interval (days to mating) in the MDMA-treated groups ranged from 3.5 to 3.9 days. Euthanasia was conducted at GD13. MDMA-related clinical observations included hypersensitivity to touch, salivation, vocalization, red material, and red discolored wet hair around the nose and/or mouth and were not considered adverse. MDMA-related

decreases in body weight, body weight gain, and food consumption were expected pharmacological effects based on repeat-dose studies described in Section 4.3.2 Repeat-Dose Toxicology Studies. Mean prostate gland weights decreased in all MDMA-treated groups relative to controls, however this did not affect fertility or overall health of the animals. The NOAEL dose was demonstrated to be the highest dose level evaluated ≤10 mg/kg/day (supratherapeutic dose) in both genders for fertility and reproductive performance.

The sponsor has completed a pilot prenatal developmental toxicokinetic study in time-mated female rats in order to optimize dose selection for planned reproductive toxicology studies (see Table 1: Summary of Completed and Planned Nonclinical Toxicology Studies). Rats were dosed on gestations days (GD) 6 through 17. Five dose levels were tested 0 mg/kg/day (vehicle control), 2.5 mg/kg/day, 5 mg/kg/day, 15 mg/kg/day and 20 mg/kg/day by gavage. Five animals were tested for each dose level. The following parameters and endpoints were evaluated in this study: clinical signs, body weights, body weight gains, and food consumption, toxicokinetic (TK) parameters, and anatomic pathology including a uterine examination. All fetuses were given an external examination. MDMA-related clinical observations of salivation, as well as decreases in mean gestation body weight, body weight change, food consumption, adjusted GD 21 body weight, and adjusted GD 6 to 21 body weight change were observed at all dose levels. MDMA-related decreases in mean gestation body weight and body weight change in comparison to controls were observed at all dose levels evaluated. At 15 mg/kg/day, mean body weight was statistically lower than controls on GD 9 (-8.8%) and 12 (-8.4%). At 20 mg/kg/day, mean body weight was statistically lower than controls on GD 9 (-10.6%) and 12 (-8.9%). MDMA was tolerated at dose levels ≤20 mg/kg/day when administered to time-mated female rats once daily via oral gavage from GD 6 to 17. No effects of MDMA at these dose levels were noted on mortality, clinical observations, or maternal macroscopic observations. Likewise, no MDMA-related effects were noted at dose levels ≤20 mg/kg/day on ovarian and uterine implantation data (mean number of corpora lutea, implantation sites, viable fetuses, resorption sites [early, late, and total], litter size, and mean pre- and post-implantation loss indices), mean gravid (pregnancy) uterine weights, or fetal body weights. No external malformations or developmental variations were noted in any of the fetuses evaluated on GD 21. As expected from prior literature, the AUC/Dose ratio increases with higher doses, indicative of non-linear pharmacokinetics. Systemic exposure (AUC0-12hr) to MDMA did not appear to change following repeated administration of MDMA, indicating lack of systemic accumulation in rats despite daily dosing. Pilot dose range finding developmental toxicity studies found no adverse developmental effects in rats at 20 mg/kg/day by gavage.

The sponsor has also completed a pilot prenatal developmental toxicokinetic study in time-mated female New Zealand White Hra:(NZW)SPF rabbits in order to optimize dose selection for planned reproductive toxicology studies (see Table 1: Summary of Completed and Planned Nonclinical Toxicology Studies). Rabbits were dosed on gestations days (GD) 6 through 17. Five dose levels were tested 0 mg/kg/day (vehicle control), 2.5 mg/kg/day, 5 mg/kg/day, 15 mg/kg/day and 20 mg/kg/day. Six animals were tested for each dose level. The following parameters and endpoints were evaluated in this study: clinical signs, body weights, body weight gains, and food consumption, toxicokinetic parameters, and anatomic pathology including a uterine examination. All

fetuses were given an external examination. MDMA-related mortality was observed at 15 and 20 mg/kg/day. Two females died on GD 7 following a single dose of MDMA at 20 mg/kg. Due to excessive toxicity at 15 mg/kg/day the dose level was lowered to 10 mg/kg/day beginning on GD 9 and the remainder of the 20 mg/kg group was euthanized. MDMA was tolerated at dose levels ≤10 mg/kg/day when administered to time-mated female rabbits once daily via oral gavage from GD 7 to 19. No effects of MDMA at these dose levels were noted on mortality, mean gestation body weight, or maternal macroscopic observations. No external malformations or developmental variations were noted in any of the fetuses evaluated on GD 29. As expected from prior literature, the AUC/Dose ratio increases with higher doses, indicative of non-linear pharmacokinetics and possible systemic accumulation in pregnant rabbits. Pilot dose range finding developmental toxicity studies found no adverse developmental effects in rabbits at 10 mg/kg/day by gavage.

4.3.6 Other Toxicity Studies

4.3.6.1 Immunological Effects

MDMA may act as a mild immunosuppressant in rodents, with no evidence of immunotoxicity in repeat-dose toxicology studies described in Section 4.3.2 Repeat-Dose Toxicology Studies. Only a trend towards a dose-dependent increase in White Blood Cells were noted in the dog study, which could be related to an increase in cortisol secretion induced by MDMA. Single-dose MDMA administration at 5 mg/kg in rats is associated with impaired macrophage activity as evidenced by inhibition of Tumor Necrosis Factor-alpha (TNF-α) secretion for 12 hours post-drug [264]. In mice injected with 10 mg/kg MDMA for 5 days, increases in in epithelial tissue of cytokines interleukin 1-alpha (IL-1α), granulocyte-colony stimulating factor (G-CSF), and interleukin 3 (IL-3) were found, while decreased serum levels of many cytokines were reported [265]. MDMA decreased neutrophil oxidative bursts and phagocytosis and increased the number of circulating neutrophils while decreasing the number of lymphocytes. Incubating photoreceptor-generated cells with 0.5, 1 and 2 µM MDMA activated macrophages and leading them to release proinflammatory cytokines [266]. MDMA also increased hypothalamus-pituitary-adrenal (HPA) axis activity through a noradrenergic pathway in the hypothalamus [267]. MDMA also suppresses interferon-γ secretion and signaling in mice [268]. Interestingly, MDMA was shown to reduce inflammation and airway reactivity in a mouse model of allergic asthma, suggesting that 10 mg/kg MDMA (i.p.) could have beneficial immunomodulatory effects in cases of heightened inflammation [269]. A microarray study found that mice self-administering MDMA at moderate doses had transcriptional changes in many genes related to immune and inflammatory responses as well as neuroplasticity and learning [270], suggesting that immunosuppressant effects of MDMA at clinically relevant doses could be beneficial in the treatment of psychoneuroimmunological disorders such as PTSD [271]. There have been no publications reporting an increased occurrence of tumors or infections associated with MDMA administration to date, so these cell-mediated effects are unlikely to relate to immunotoxicity.

4.3.6.2 Mechanistic Studies

Epigenetic modifications, including deoxyribonucleic acid (DNA) methylation, demethylation, and histone acetylation, are thought to be involved in dynamic regulation of memory reconsolidation in the adult nervous system and play a role in memory formation [272]. Early childhood adversity and trauma is associated with transcriptional silencing of the Brain Derived Neurotrophic Factor (BDNF) gene through DNA methylation, which can either be a risk factor in development of PTSD or a result of having PTSD in adulthood [273]. Epigenetic effects on BDNF and other gene expression is one possible hypothesized mechanism by which MDMA in combination with training in animal studies modeling anxiety disorders, or psychotherapy in humans, exerts its therapeutic effects.

The social effects of MDMA may also include setting-dependent acute social sensitization and extension of a critical period of increased sociality in mice. MDMA may sensitize mice to social interactions with unfamiliar mice via setting-dependent sensitization [274]. After an initial dose of MDMA (7.8 mg/kg) in the company of an unfamiliar mouse, a subsequent dose produced greater social interaction. The same effect did not occur when preceded by a social setting, or with MDMA in a nonsocial setting, and the effect can be antagonized by blocking 5HT2A receptors. Adult mice exhibited a greater desire to be with another mouse 2 days after receiving MDMA (10 mg/kg) [275], re-opening a critical period for learning social reward that generally declines during adulthood. This effect appears tied to upregulation of oxytocin receptors in the nucleus accumbens. These effects may support posited therapeutic effects in humans, such as increased rapport with therapists and greater ability to have fulfilling interpersonal relationships.

A series of studies examining neuritogenesis, a marker of neuroplasticity, found that MDMA and classic psychedelics stimulated neurite growth [276], with this BDNF-dependent effect blocked by 5HT2A antagonists. MDMA was more efficacious than ketamine in promoting neurite growth. These findings may lie behind some of the therapeutic effects of MDMA, such as enhanced fear extinction learning, greater sensitization to prosocial effects and or re-learning or re-opening experiencing social reward, but behavioral effects were not specifically tested in this report.

MDMA given before training persistently enhanced fear extinction learning in mice through a BDNF-dependent mechanism [277], which could be a possible mechanism of action for MDMA in combination with psychotherapy as a treatment for anxiety disorders. The dose of 5.6 mg/kg was approximately two times a human equivalent dose based on exposure, but these findings were the first biological evidence of a lasting effect of MDMA administered in combination with training on lasting attenuation of anxiety-related behavior in mice. MDMA, (1 mg/kg, 2.5 and 5 mg/kg, not 1 or 10 mg/kg) given alone or with nicotine, enhanced consolidation of recall for a passive-avoidance task, a different type of fear memory [176, 278]. A fear extinction study in rats funded by MAPS failed to replicate an enhancement of fear extinction, finding instead that 3 and 5 mg/kg MDMA administered prior to training impaired fear extinction learning, while MDMA administered during reconsolidation produced persistent reduction in fear [279]. These

results highlight species-specific differences between rats and mice among translational mechanistic studies attempting to simulate results observed in clinical trials.

A number of research teams have studied the effects of MDMA on gene expression in rodents [280-285]. Many of these reports used 10 to 20 mg/kg MDMA, a dose range that is 5 to 10.7 times greater than the 1.5 to 2 mg/kg doses employed in human trials. Toxicity was not observed at these doses, and effects were broadly indicative of changes in memory and cognition. Particularly of interest for treatment of PTSD, one study found downregulation of the gene for several glutamate receptor genes, several calcium transport genes, and the cannabinoid receptor CB1, among other effects [281]. Another study found that MDMA influenced genes of proteins known to regulate glutamatergic signaling and are associated with neuroplasticity and learning, as well as processes involved in memory consolidation in serotonergic neurons [270]. These studies also report an increase in expression of genes that regulate the GABA transporter [280], which is expressed in GABAergic neurons indirectly regulated by glutamatergic afferent neurons. Serotonin-transporter knockout mice did not display some of these changes in gene transcription, suggesting that serotonin release is required for this activity [280]. In the acute period 24 to 48 hours after MDMA exposure, a study in rats found 33 to 70% upregulation of BDNF messenger ribonucleic acid (mRNA) transcripts in the frontal cortex, with a time-dependent decrease, up to 73%, of BDNF transcripts in the hippocampus [286]. The frontal cortex and hippocampus are both regions known to play a causal role in memory retrieval and reconsolidation in animals and humans [287], mediated in part through GABAergic signaling [288]. Changes in transcription do not always correlate with functional consequences in proteins levels. BDNF has been shown to have multiple functionally distinct splice variants which have tight temporal and spatial control in an activity-dependent, stimulus-specific manner [289]. However, MDMA produces a durable enhancement of fear extinction in mice, an effect mediated by an MDMA-associated increase in BDNF expression specifically in the context of fear extinction training, supporting that gene expression changes after MDMA are functionally relevant [277].

Examining rat brains after repeated MDMA administration for 2 weeks detected a sharp drop in SERT expression [290], suggesting a compensatory downregulation in response to repeated high doses of MDMA. A study in rats found repeated administration of MDMA at 1 or 5 mg/kg weekly for 4 weeks increased transcripts for 5HT1B receptors in various brain regions and 5HT2C receptors in the cortex and hypothalamus, likely due to serotonin depletion and subsequent need to increase serotonin receptor availability [291]. Increased levels of gene transcripts regulating extracellular signaling in mice were also reported after MDMA [292]. Serotonin may play a more significant role than dopamine in transcription changes mediated by MDMA [291]. Mouse brains examined 8 hours after 8 days of self-administration or non-contingent administration detected increased transcription of genes related to inflammation and immune modulation in both groups and transcription of genes related to neuroadaptation in mice self-administering MDMA [270]. Transcripts in these studies were assessed 8 to 10 hours after the last of repeated MDMA administrations and it is unclear whether these changes reflect residual acute effects of the MDMA, or changes related to repeated MDMA administration. Findings in rats were confirmed in humans receiving a dose of 75 mg MDMA in the therapeutic dose range, which found increased expression of the SERT gene after MDMA when compared

with placebo [293]. Increased SERT gene expression after MDMA was associated with decreased arousal and increased fatigue. Taken together, these nonclinical studies support a plausible mechanism for the therapeutic actions of MDMA administered in a single-dose regimen.

4.3.6.3 Abuse Potential

Nonclinical studies support that MDMA possesses abuse potential, to a much lesser degree than amphetamine. A number of studies have investigated the abuse liability of MDMA in animals through paradigms of drug seeking, drug discrimination, and withdrawal. Mice, rats, and monkeys self-administer MDMA, indicating that MDMA has rewarding properties in animals [294-297]; however, the rate and response-acquisition of self-administration is much lower than other drugs of abuse, such as cocaine or heroin. Rodent studies found that training attempts at self-administration required an increased training dose of 1.75 mg/kg for acquisition over a 5 week period [296, 298-300]. Research that used rate of self-administered intracranial self-administration (ICSS) as a measure of abuse liability, and comparing response to 0.32, 1, or 3.2 and 3 mg/kg MDMA in male and female rats reported that MDMA increased responding for ICSS when the rate of responding for ICSS was low, and reduced seeking ICSS when rate of responding was very high in both sexes [118].

Physical dependence and drug withdrawal were investigated by treating rats with 10 mg/kg i.p. MDMA twice daily for 5 days. When compared with rats trained to self-administer cocaine, MDMA-trained rats were less likely to return to self-administration after a period of abstinence [295]. Results in a study in mice showed that they did not exhibit aversive/dysphoric or anxiogenic behaviors after treatment, indicating that high doses of MDMA do not induce classical symptoms of physical dependence [301]. Monkeys choose to self-administer MDMA in doses equivalent to or only slightly higher than doses used by humans [294], but typically reduce their MDMA intake over time. While monkeys work hard to obtain MDMA, they work harder to obtain other psychostimulants, such as cocaine or methamphetamine [299, 300]. Taken together, results in animals suggest that the abuse liability of MDMA is low to moderate.

Nonclinical drug discrimination studies investigating the discriminative stimulus effects of MDMA as either hallucinogenic or stimulant have reported inconsistent findings, indicating that psychoactive effects of MDMA are not expressly hallucinogenic or stimulating [302]. Two-way discrimination studies with MDMA are not specific enough to assess the complex pharmacological profile of MDMA and lead to low accuracy and mixed results. In three-way discrimination studies, MDMA has discriminative stimulus effects that are more serotonergic, with minimal involvement of dopamine. One such study found that lysergic acid diethylamide (LSD) produced dose-dependent increased substitution for MDMA while neither cocaine nor 2,5-dimethoxy-4-bromoamphetamine (DOB) substituted for it [303].

Administering MDMA to amphetamine-trained rats suggests that dopamine plays a role in stimulus properties, but blocking serotonin receptors interfered with recognizing MDMA, while administering dopamine receptor antagonists did not do so [304]. A higher dose of 3 mg/kg may have a greater dopaminergic component, while 1.5 mg/kg

may have more of a serotonergic component [130] in drug discrimination studies in rats. Serotonin 5HT1A-acting drugs were treated similarly to both 1.5 mg/kg and 3 mg/kg MDMA [130]. Drug discrimination studies in SERT knockout rats supports a key role for serotonin release in producing the subjective effects of 1.5 mg/kg MDMA [143]. The ratio of serotonin to dopamine release are likely to influence stimulus characteristics of MDMA in animal models, and these studies lead to the definition of a unique class of drugs called the Entactogens, which are clearly distinguishable from hallucinogens and stimulants. Discrimination research in a sample of monkeys trained to discriminate cocaine from saline and tested with cathinones, amphetamines, and MDMA and MDA, suggested that the greater serotonergic effects of MDMA are at least partially related to the methylenedioxy structure [305].

5.0 Epidemiological and Naturalistic Evidence Summary

Evidence exists for intentional human use of MDMA in the late 1960s [49]and there are records of a police seizure of MDMA in the early 1970s [306]. An estimated 500,00 doses of MDMA were administered in a psychotherapeutic setting prior to MDMA being in Schedule I [49, 307]. MDMA was administered to thousands of people prior to scheduling and many continue to use Ecstasy around the world in various non-medical settings [64, 189, 308-310]. In this IB, 'Ecstasy' refers to material assumed to be MDMA used in naturalistic settings, however when used in these uncontrolled settings, the drug may not contain any MDMA and is likely to be of limited purity. It may contain other substances along with or instead of MDMA, and when present, the amount of MDMA can vary widely [311-313]. These synthesized tablets may also be cut or mixed with other psychoactive substances. Substances found mixed with MDMA have included amphetamine methamphetamine, dextromethorphan, paramethoxymethamphetamine (PMMA), paramethoxyamphetamine (PMA), cathinones, ketamine, caffeine, and ephedrine [313, 314]. Most studies rely on self-reported use and do not attempt to confirm that material contained MDMA. Retrospective studies, epidemiological settings and case reports of morbidity and mortality in Ecstasy users are summarized in Section 5.1 Serious Reports of Incidents, Mortality, and Morbidity.

It is important to note that the vast majority of non-clinical epidemiological studies are retrospective comparisons of people who have previously self-administered Ecstasy, a study design that is unable to eliminate the possibility that one or more predisposing factors may lead to repeated Ecstasy use [79, 310, 315]. Samples are often selected on the basis of moderate to heavy self-reported Ecstasy use, with very few studies conducted in samples reporting the levels of moderate exposure seen in clinical trials. Many of these studies have compared people reporting use of Ecstasy with non-Ecstasy using controls, mostly as a means of detecting long-term effects of Ecstasy use, and do not appropriately match samples for polysubstance use. Findings are considered cautiously with respect to their degree of relevance for safety in clinical trials.

5.1 Serious Reports of Incidents, Mortality, and Morbidity

Numerous serious events, including fatalities, have been reported in humans after Ecstasy use in unsupervised and uncontrolled settings. These events are relatively rare given the widespread prevalence of Ecstasy use (an estimated 4% of people, or roughly 13.7

million people, ages 15 to 64 in Europe to 6.7%, of people ages 12 and older in the US) [316, 317]. The UN World Drug report concluded that an estimated 20.5 million people (0.4% of the global population) had used 'Ecstasy' at least once in in 2018 [318]. These include hyperthermia (potentially arising from "serotonin syndrome"), psychiatric problems, hepatotoxicity (secondary to hyperthermia), cardiac disorders and hyponatremia [80, 316, 319-321]. Set and setting likely play a role in the development of some Ecstasy-related adverse outcomes, such as vigorous exercise, lack of attention to somatic cues, and too little or too much hydration combined with pharmacological action on oxytocin and/or AVP resulting in hyperthermia or hyponatremia [322, 323]. A systematic search of medical literature was conducted using the PubMed database on April 1, 2020 and using the Boolean expression "MDMA AND Ecstasy AND human." The reports of serious morbidity and mortality where MDMA was detected in plasma or other fluids are summarized in Table 3 below.

Most Ecstasy-related emergency department admissions are the result of people experiencing anxiety or panic reactions after use and were treated with supportive care [320, 324, 325]. An extensive systematic review reached similar conclusions concerning the frequency and nature of emergency department admissions, though also noting that owing to complexities of nonmedical and recreational use, the researchers found it hard to establish a lethal dose [80]. However, a pair of case series drawn from two different events suggests a general relationship between estimated dose and number of emergency department admissions after exhibiting seizures, unresponsiveness or hyperthermia, with both series reporting high doses of MDMA (230 and 270 mg) in sample tablets or capsules [326, 327]. Post-mortem hyperthermia due to a deadly intoxication by Ecstasy was found in a 19-year old female. Toxicology results showed the presence of MDMA with a lethal blood concentration of 4.52 mg/mL and detection of cannabinoid with a blood concentration to 0.7 ng/mL. The MDMA concentration was 8.96 mg/mL in the bile and 129.7 mg/mL in the gastric content. The blood alcohol concentration was 0.8 g/L [328]. As is the case with fatalities associated with reports of Ecstasy use, medical emergencies after Ecstasy use are more likely to occur in men [320]. Individuals consuming Ecstasy with pre-existing conditions are at increased risk when consuming drugs of unknown purity, identity, and dose in uncontrolled settings.

Table 3: Summary of Published Morbidity and Mortality Reports

Body System	Reports	Morbidity Reports	Mortality Reports	Total Reports
Thermoregulatory Disorders (MedDRA "Body Temperature Conditions" under "General Disorders and Administration Site Conditions)	Hyperthermia, Hyperprexia, (sequelae incl. Rhabdomyolysis, seizure, Hypoglycemia)	137 [69, 326, 329-345]	46 [69, 168, 326, 329, 341, 346, 347] [328, 348]	183

Cardiac Disorders	Cardiac valve disease, Ventricular fibrillation, Cardiac arrest, Arrythmia, Myocardial infarction, Generalized tonic-clonic seizure, Acute coronary syndrome, Myocardial necrosis, Cardio-respiratory arrest, Cardiomyopathy	15 [349-357]	12 [329, 358-363]	27
Metabolism and Nutrition Disorders	Acute renal failure, SIADH, Urinary retention, Hyponatremia, (sequelae of cerebral oedema, Acute renal failure), Diabetic ketoacidosis (MDMA+alcohol)	19 [364-376] [377]	7 [349, 378-383]	26
Hepatobiliary Disorders	Acute fulminant hepatitis, Liver disease, (Sequelae: Disseminated intravascular coagulation)	4 [357, 384-386]	5 [387-391]	9
Blood and Lymphatic System Disorders	Aplastic anemia	3 [392, 393]	1 [394]	4
Injuries, Poisonings, and Procedural Complications	Anaphylactic shock, Facial rash eruption, swollen lip (allergic or mechanical injury)	2 [395, 396]	1 [397]	3
Nervous System Disorders	Hemorrhage, Infarct, Hippocampal sclerosis (suspected), Encephalopathy, Leukoencephalo -pathy Amnestic syndrome	15 [398-409]	0	15
Gastriointestional Disorders	Xerostomia, Bruxism, Dental erosion	15 [410-412]	0	15
Psychiatric Disorders	Psychotic episode, Depressive episode, Obsessive-compulsive disorder, Auto-enucleation	4 [413-415]	0	4
Respiratory, Thoracic, and Mediastinal Disorders	Subcutaneous Pneumomediastinum, Epidural pneumatosis, Diffuse alveolar hemorrhage, Asthma Airway necrosis	9 [360, 416-423]	1 [424]	10

Eye Disorders	Lagophthalmos, Keratopathy, Bilateral sixth nerve palsy	4 [425, 426]	0	4
Injuries, Poisonings, and Procedural Complications	Unknown cause of death Heat stroke*	0	207 [360, 427] [428]	207
Skin and Subcutaneous Tissue Disorders	Angioedema	1 [429]	0	1
Vascular disorders	Ischemia in person with myocardial bridging	0	1 [430]	1
Total Reports		500	279	679

*MDMA detected in blood of three fatalities but authors viewed as heat stroke resulting from combination of environmental condition (outdoor music festival in tropical climate) combined with drug use.

Five hundred case reports of morbidity and 279 reports of morbidity associated with Ecstasy use from 1986 through 2018 are summarized in Table 3. Of these 279, 32 were described in a cumulative 2002 literature review with incomplete citations of sources, and are conservatively reported in addition to individual case reports of morbidities in the literature [329]. Detectable levels of MDMA in blood or urine are reported in less than half of these case reports, and range from 50 ng/mL (reported as less than 0.05 mg/L) in the case of anaphylactic shock [397] to 1500 ng/mL (reported as 1.5 mg/L) in a fatal case of hyperthermia and rhabdomyolysis [347].

Assessment of brain and blood MDMA in 11 fatalities under forensic autopsy detected lower doses in deaths where MDMA was determined to be incidental (accident, homicide) or detected in combination with other drugs versus blood and brain levels in a pair of deaths where cause of death was MDMA and no other drugs [431]. It is more difficult to associate events with MDMA when the compound is not detected or when detection is for amphetamines in general. Some events, such as valvular heart disease (VHD), acute hepatitis with gallbladder inflammation, liver disease, or urinary retention occurred in individuals who self-reported daily use for months to years prior to the event. In the majority of the 202 poisoning cases with unknown cause of death in the UK and Wales between 1996 and 2002, Ecstasy was used in combination with opiates [427]. Polysubstance use is common in the majority of serious reports presented.

5.1.1 Thermoregulatory Disorders

Thermoregulatory disorders play a part in the development of a constellation of disorders across body systems. Primary symptoms are hyperthermia resulting in rhabdomyolysis described in 137 reports of morbidity and 46 reports of mortality, constituting the most common acute and serious adverse effect associated with Ecstasy [80, 432]. Thermoregulatory effects of Ecstasy taken in epidemiological settings are highly dependent on dose [432, 433] and permissive factors, including high ambient temperature [434, 435], crowded conditions involving overwhelming social interaction, physical exertion, reduced fluid intake [434], and thyroid dysregulation [436, 437]. Sympathomimetic effects of MDMA, at unknown doses and purity, in combination with permissive factors in uncontrolled settings, can lead to serious reports of acute and persisting adverse effects on multiple organs. In research settings, the risk of

hyperthermia is limited by controlling ambient temperature, conducting treatment sessions in relaxed, private environments, and generally limiting permissive factors.

5.1.2 Cardiac Disorders

Cardiac disorders associated with Ecstasy in the context of hyperthermia resulted in 15 reports of morbidity and 12 reports of mortality. Several fatal cases of cardiac arrest were reported. The elevation of blood pressure and increased heart rate produced by MDMA, similar to that produced by other sympathomimetic drugs, can lead to additional risks and complications [399, 400, 438], such as stroke, cardiac events, or other cerebrovascular events, including cerebral venous sinus thrombosis [439] and cerebral or subarachnoid hemorrhage [69, 440-444]. In two such cases, a previously existing underlying arteriovenous malformation appeared to play a role in the event [440, 442]. Intra-cardiac pressures, intra-arterial pressures, angiotensin II, pain, and adrenergic (α2) central nervous stimuli can also influence AVP secretion [445]. Increased AVP concentration, which is also caused by MDMA as described in Section 6.2.3.2 Cardiovascular System, is described in several studies as a strong predictor of mortality in patients with chronic heart failure and acute heart failure, and contributes to increases in blood pressure [446]. As with any amphetamine, increased heart rate (tachycardia) and elevated blood pressure can also lead to cardiac events, such as arrhythmias or myocardial infarction [349, 360]. Fatal dysrhythmias have been reported following heavy MDMA use, resulting in ventricular fibrillation and asystole. Individuals with underlying cardiac and/or pulmonary disease and preexisting conditions such as Wolff-Parkinson-White syndrome are especially at risk for heart failure and fatal arrhythmias. 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.

Some researchers have expressed concern that MDMA activity at 5HT2B receptors might be indicative of increasing risk of valvular heart disease with repeated use [30]. Studies in Ecstasy users indicated that only people reporting average lifetime exposure of 900 tablets had cardiac abnormalities indicative of potential VHD [447], and a case of VHD has occurred in a man reporting approximately 16 years of heavy Ecstasy use, from age 17 to 33 years old. [356]. No abnormalities were found in people reporting lifetime exposure of approximately 200 tablets in the same study. Valvular heart disease (VHD) only occurred after extremely heavy Ecstasy use. Ecstasy can alter cardiac function leading to rhythm disturbances and sudden death [448]. However, echocardiographic readings in eight Ecstasy users failed to find any cardiac abnormalities [40].

A non-fatal cardiac arrest occurred in the context of a genetic arrhythmia disorder, catecholaminergic polymorphic ventricular tachycardia [351]. Apparent use of Ecstasy, with concurrent use of other amphetamines during pregnancy, was associated with seizures and myocardial infarction [354, 355]. As evidenced by these reports, individuals consuming Ecstasy with pre-existing conditions that can influence cardiovascular and cardiac function are at increased risk when consuming drugs of unknown purity, identity, and dose in uncontrolled settings.

5.1.3 Metabolism and Nutrition Disorders

Disorders classified as 'Metabolism and nutrition disorders' associated with Ecstasy in the context of hyperthermia resulted in 19 reports of morbidity and seven reports of mortality, with acute renal failure (ARF) as the most common cause of death. Ecstasy use has been associated with acute symptomatic hyponatremia with the syndrome of inappropriate antidiuretic-hormone secretion (SIADH) involving raised antidiuretic-hormone, also known as AVP [228]. AVP plays a key role in osmoregulation, and is released upon a change in plasma osmolality [230]. AVP is also involved in the response and adaptation to stress, through its effects on the HPA axis [230]. The rise in AVP results from a pharmacological effect of MDMA compounded by excessive fluid ingestion [231]. SIADH refers to disorders related to water and sodium balance characterized by the impairment of urinary dilution and hypotonic hyponatremia in the absence of renal disease or other identifiable non-osmotic stimuli known to activate the release of AVP [229].

In Ecstasy users with confirmed urinary MDMA, a significant association was found between plasma osmolality, plasma sodium, and CYP2D6 extensive metabolizer/ intermediate metabolizer genotypes and COMT low-activity genotypes [449]. Effects of Ecstasy, combined with increased consumption of water and permissive factors, such as strenuous exercise in warm ambient temperatures, can be further exacerbated in the context of poor metabolism. Gauging appropriate water intake may be difficult for users to estimate because MDMA reduces perception of thirst and impairs judgment [450].

A number of case reports describe hyponatremia after uncontrolled, non-medical Ecstasy use [321, 322, 451, 452]. A recent meta-analysis showed that a moderate reduction of serum sodium concentration is associated with an increased risk of death in different pathologic conditions [453]. Relationships have been found between reduced plasma sodium, a measure of hyponatremia, and variations in COMT and CYP2D6 genotypes, possibly related to increased AVP and oxytocin release associated with MDMA [449]. Active doses of MDMA likely inhibit CYP2D6 in most individuals, as described in Section 6.2.1 Pharmacokinetics and Product Metabolism in Humans. Behavioral factors, including vigorous exercise and excessive consumption of water without an attempt to replace electrolytes, and an increase in the anti-diuretic hormones AVP and oxytocin, likely all contribute to this very rare but serious condition in Ecstasy users [454]. Women are generally more likely to exhibit hyponatremia than men [455, 456], including Ecstasy or MDMA related hyponatremia [321]. Heart failure is commonly associated with hyponatremia, and is also characterized by increased concentrations of AVP [457-459].

Increased AVP secretion caused by MDMA in combination with permissive factors in uncontrolled settings can lead to serious reports of acute and persisting adverse effects on multiple organs, including the liver. Individuals consuming Ecstasy with pre-existing conditions that can influence renal function are at increased risk. In response to this risk, many users tend to overcompensate with excessive consumption of water, leading to dilutional hyponatremia. Prevention of hyponatremia with limited consumption of electrolyte containing fluids and controlled ambient temperatures are required to preserve the body's homeostatic maintenance of fluid balance.

A patient with Insulin-dependent diabetes mellitus consumed alcohol and Ecstasy which caused diabetic ketoacidosis [383]. An autopsy revealed microhemorrhages in the brain with subnuclear vacuolization and Armanni-Ebstein changes in renal tubes. A low level of MDMA was found in the blood (<0.01 mg/L).

5.1.4 Hepatobiliary Disorders

Hepatobiliary disorders associated with Ecstasy use resulted in four reports of morbidity and five reports of mortality. One of the mortality reports happened 1 week after Ecstasy use and was consistent with acute fulminant hepatitis in the absence of viral infection. This patient died despite liver transplantation efforts [387]. Typically, mortality results from disseminated intravascular coagulation (DIC) caused by platelet dysfunction associated with liver failure. Non-fatal morbidity reports range from acute hepatitis associated with daily usage of five to eight tablets of Ecstasy for 3 months in combination with alcohol [384] to liver damage in combination with congestive cardiomyopathy [357]. Given that polysubstance use and prior insult to liver function cannot be ruled out, the frequency of isolated serious hepatotoxicity cases in the absence of hyperthermia are rare among serious reports associated with Ecstasy use. Hepatotoxicity is more common among serious reports in combination with hyperthermia and acute renal failure.

5.1.5 Blood and Lymphatic System Disorders

Blood and lymphatic system disorders associated with Ecstasy use resulted in three morbidity reports and one mortality report of aplastic anemia. The death after aplastic anemia occurred from complications of immunosuppressant therapy followed by an allogenic stem cell transplant, 17 months after the first admission [394]. The patient had initially presented with progressive weakness and epistaxis, resulting from daily Ecstasy use for 7 months, combined with heavy alcohol intake. Further examination revealed the replacement of bone marrow tissue with fatty deposits, likely due to alcohol consumption and exacerbated by chronic Ecstasy use. Three reports of morbidity ranged in prior Ecstasy use levels from one to four times in the prior year, with two cases spontaneously resolving within 2 months and the treated case failing immunosuppressive therapy and recovering 4 months after subsequent bone marrow transplant [394].

5.1.6 Injuries, Poisonings, and Procedural Complications

A report of possible anaphylactic shock and subsequent death occurred in a 13-year old girl who had at least one previous exposure to Ecstasy [397]. Her friends reported that she experienced swelling lips after her first exposure. After approximately 1.5 tablets, the girl experienced nausea and vomited, and later had difficulty breathing. On admission she was hypothermic and hypotensive. A low level of MDMA (<0.5 mg/dL) was detected in blood. None of the other individuals consuming tablets from the same batch underwent similar experiences. Autopsy found a massive brain edema as well as laryngeal oedema and lung congestion. Chemical analyses ruled out hyponatremia. The reaction may have been to MDMA or to an adulterant in the tablet. The authors of the report do not report whether tablets were assessed for contents. A report of swollen lips in a woman with detectable levels of MDMA in blood (1.466 mg/L) is ambiguous as to cause of swelling,

since the patient may have experienced a sexual assault and injuries in transit to ER, and cannot clearly be established as an allergic reaction [396].

5.1.7 Gastrointestinal Disorders

Gastrointestinal disorders resulted in 15 reports of morbidity including xerostomia, bruxism, and dental erosion in the context of Ecstasy use. Between 93 to 99% of Ecstasy users experience dry mouth or xerostomia at higher doses for up to 48 hours after consumption of Ecstasy, which can lead to enamel erosion [410]. Jaw clenching and grinding of teeth is frequently reported during Ecstasy use as well as in clinical trials. Tooth wear through the enamel into the underlying bone occurred in 60% of Ecstasy users versus 11% of non-users in one study, which was attributed to jaw clenching rather than tooth grinding [410]. Necrotising gingivitis and tenderness in the temporomandibular joint were also reported.

5.1.8 Respiratory, Thoracic, and Mediastinal Disorders

Respiratory, thoracic, and mediastinal disorders resulted in 9 reports of morbidity and one report of mortality in the context of Ecstasy use. A single mortality report of airway necrosis occurred in a 25-year-old male who had a history of occasional Ecstasy use by inhalation. The patient was initially found unresponsive and was resuscitated, but airway necrosis due to vasoconstriction of airway walls led to hypoxic cardiac arrest [424]. This report is not consistent with the usual respiratory, thoracic, and mediastinal adverse outcomes reported from oral administration of Ecstasy. The mortality report is likely due to the patient's chosen route of administration.

5.1.9 Psychiatric Disorders

Psychiatric disorders associated with Ecstasy use resulted in 4 morbidity reports and no mortality reports. 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 a common reason for appearance at an emergency department [451]. 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 included panic, restlessness and psychotic response, as seen a systematic review and several epidemiological case series [80, 460]. 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 pre-existing psychiatric problems occur in people who choose to use Ecstasy [461] 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 [320, 325]. 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 symptoms of depression or anxiety [462, 463]. A meta-analysis of self-reported depressive symptoms

detected an association between Ecstasy use and self-reported depression symptoms [464]. However, the association was strongest in studies with small samples, and drug use variables were often incompletely reported and not verified. 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 [465-468]. Two studies found an equal or stronger association between regular use of cannabis, and not Ecstasy, with anxiety, depression or other psychological problems [469, 470]. An assessment of men reporting substance use in a large cohort found that the highest degree of mental health problems in respondents reporting Ecstasy use in the last 12 months, followed by those reporting stimulant use [471]; stressful life events and perceived stress also differed across groups. Anxiety regarding loss of control under the influence of Ecstasy could develop to a degree where it could lead to panic attacks. Case reports have been published describing panic attacks in individuals under the acute influence of Ecstasy [472]. Enduring panic attacks have been reported in individuals after repeated Ecstasy use [473, 474] and in one case, even after a single dose [475].

When compared with polydrug using controls, people who use Ecstasy report being more empathetic and exhibit greater cognitive empathy when viewing photographs of expressive emotions [476], and did not differ in degree of reaction to social exclusion. These findings may be affected by the same problems as other retrospective studies, such as the presence of another factor or factors influencing empathy and drug use patterns.

Neuroendocrine response to oral citalopram did not differ between Ecstasy users, cannabis users and controls [477]. People reporting regular drug use and Ecstasy use had higher levels of salivary cortisol in the evening, and higher salivary cortisol on the day of a multitasking activity [478], and higher salivary cortisol on waking that was unrelated to prefrontal SERT binding or self-reported depression symptoms [479]. A 4-year longitudinal study reported that factors other than Ecstasy use, including female gender and presence of financial and relationship difficulties, were more closely related to self-reported symptoms of depression [480]. Comparison of self-reported psychological symptoms in samples of people grouped by self-reported drug use found current Ecstasy users had lower global symptom severity scores than polydrug users [481]. In conclusion, it appears that the relationship between Ecstasy use on self-reported mood or psychiatric problems is not strong, with equal or stronger involvement of other factors.

5.1.10 Nervous System Disorders

Nervous System disorders associated with Ecstasy use resulted in 15 morbidity reports and no mortality reports. Memory difficulties arising immediately after Ecstasy use have been reported in a sporadic user [404]. The memory difficulties arose in a man reporting use of Ecstasy five or six times, with confusion and cognitive impairment reportedly occurring after taking a single tablet at a party. Cognitive function was assessed 7 years later. Imaging showed signs of hippocampal sclerosis. It is not clear from the report whether the individual used Ecstasy prior to or after this event. The individual had hypertension, raising questions concerning possibility of a cerebrovascular event. In a report of a serious neurological event with 0.83 ng/mL MDMA detected in the hair of a girl who developed encephalopathy [403] during chronic low or moderate Ecstasy use, cognitive function and memory problems associated with neurological damage was

reported. Upon cessation of use 16 months later, extensive hippocampal remodeling was reported assessed through positron emission tomography (PET) scans. This finding is consistent with hippocampal dendritic spine remodeling observed in rats receiving 20 mg/kg MDMA for 4 days intended to simulate chronic usage in humans [482], however, the clinical presentation was also similar to CNS herpes infection, so it is difficult to attribute this isolated case report to only Ecstasy use. Two reports have identified bilateral lesions in the globus pallidus of Ecstasy users during magnetic resonance imaging (MRI) or autopsy, with a third report finding hippocampal changes in imaging associated with amnestic syndrome [405-407]. Due to the retrospective and infrequent nature of these reports, it is difficult to determine causality.

Many researchers have studied the effects of repeated non-medical or recreational use of Ecstasy in humans [72-74, 483]. Early investigations had several methodological flaws, including retrospective design and poor matching of Ecstasy users with appropriate controls [79, 484]. Later studies sought to remedy some of these problems by using carefully matched polydrug user or cannabis user controls, or by relying on a sample with relatively low exposure to psychoactive substances, including alcohol [485-488]. Researchers comparing the average reported Ecstasy/MDMA use of samples in imaging studies with average use in a large, global internet survey found participants in imaging studies were in the top 5 to 10% in terms of size of usual dose and amount taken per occurrence [489]. Imaging studies may not represent effects in people reporting average use, or in people enrolled in clinical trials. Some of these investigators also conducted longitudinal studies, comparing Ecstasy users, sometimes alongside controls, at two separate time points [490-492]. Retrospective studies comparing Ecstasy users with various control groups have investigated brain serotonin, sleep architecture and quality, verbal memory and executive function. Most, but not all, detect at long-term deleterious effects in samples of people who use Ecstasy. Retrospective designs, compounded with lack of information concerning exposure and insufficiently matched controls, limits their interpretability.

Most studies have suggested that heavy, but not moderate, Ecstasy users had impaired verbal memory and lower numbers of estimated SERT sites, assessed via imaging with radioactively labeled ligands in positron emission tomography (PET) or single photon emission tomography (SPECT), with heavy use often defined as 50 or more times or tablets. Taken together, findings from these studies suggest there is some risk of long-term effects in heavy Ecstasy users with respect to number of estimated SERT sites in specific brain areas and performance on measures of memory. However, interpreting findings of changes in serotonin receptors or cognitive function after repeated Ecstasy use are complicated by the possible impact of polydrug use and other potential pre-existing factors in retrospective reports, and the findings are not readily transferrable to use of MDMA in a therapeutic or research context.

5.2 Cognitive Function and Performance

Many investigations have examined cognitive function in Ecstasy users with the goal of demonstrating long-term effects of purported neurotoxicity of Ecstasy. 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 might be a significant effect of Ecstasy use on verbal memory, and a lesser effect on visual memory [80].

Retrospective designs and inappropriately matched samples continue to appear in the literature [493-495], even when using multiple control groups. Two meta-analyses of memory in Ecstasy users arrived at somewhat contradictory conclusions [496, 497]. 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 [496], 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 [497].

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 [498]. 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 participants in Schilt's study with controls, and failed to find any significant differences in working memory and selective attention [499]. An analysis of findings from largely retrospective studies of Ecstasy users reported a small deficit in verbal or working memory [80]. Retrospective studies of polydrug users who use Ecstasy and controls reported impaired global motion processing without changes to local processing [500].

Not all studies report that Ecstasy users fare worse on measures of cognitive function than controls, and methodological critiques and at least one commentary and review discuss the contribution of research and publication bias in driving findings [501]. Several reports detected little or no significant differences between Ecstasy users and polydrug user controls in performance on tasks of cognitive function [315, 499, 502-507], though other studies continue to find consistent differences, particularly in verbal memory [508-512]. Regular use of many substances, including alcohol, may affect cognitive function, with Ecstasy being only one of those substances [513]. Several reports have found relationships between cognitive function and use of other drugs as well as or instead of Ecstasy [502, 504, 508, 514-516]. The only study attempting to address effects of Ecstasy use on cognitive function in middle aged versus younger users did not find a greater degree of impairment [517].

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 [518], but found no significant relationship between lifetime Ecstasy use and visuospatial task performance. A longitudinal study comparing people who continued to use Ecstasy with those who did not do so detected lower performance on immediate and delayed visual memory [519]. In a second follow-up in the same sample reported lower scores in visual memory, at marginal significance and no further impairment [520]. An examination of the relationship between elements of Ecstasy use history and verbal memory reported that use in the past year, especially in men, was associated with impaired verbal memory [521]. The authors suggest that gender

differences in polydrug use may be involved. A study comparing performance on a test of verbal memory in 65 Ecstasy users enrolled in clinical trials of MDMA and an equal number of age and gender matched non-drug using controls from other trials failed to detect significant differences between the two groups [522].

The nature and strength of the association between regular Ecstasy use and any impairments in executive function remains inconclusive, with studies reporting conflicting results [310, 487, 488, 523, 524]. Findings from a study published in 2014 did not find differences in multitasking [478]. A meta-analysis comparing executive function in Ecstasy users and non-Ecstasy using controls found a significant effect of Ecstasy use on one component of executive function (updating), no effect on another (shifting), and mixed results when looking at other components (response inhibition and access to long-term memory) [525]. Polydrug use likely contributes to findings of impaired executive function seen in Ecstasy users [467, 526]. Current research has not settled the question.

The relationship between Ecstasy use and impulsivity has also been extensively examined, with some researchers reporting greater impulsivity in Ecstasy users and others failing to find any differences [73, 527]. Studies using both behavioral and self-report measures of impulsivity reached contradictory conclusions [506, 528, 529]. Two studies using the same measure of behavioral impulsivity in samples of heavy Ecstasy users obtained different findings [506, 528]. It is notable that Quednow and colleagues compared Ecstasy users with abstinent cannabis users and drug-naïve controls while Roiser and colleagues compared Ecstasy users with former Ecstasy users, polydrug users and drug-naïve controls, raising the possibility that results might have differed in part due to control group selection. It is possible that people who self-administer Ecstasy may already possess above-average levels of sensation-seeking and impulsiveness. To date, all such studies have used retrospective study designs and cannot rule out this possibility, and some studies suggest that polydrug use may be equally or more strongly related to impulsivity in Ecstasy users [530-532]. A systematic review of decision-making that addressed many of these studies concluded that the current research does not permit drawing conclusions concerning effects of long-term Ecstasy use on decision-making [533]. Adolescents "at risk" for stimulant use, including MDMA, reported greater rates of gambling than at-risk adolescents not reporting stimulant use, with gambling considered a possible marker of impulsivity [534]. The relationship between drug use, including Ecstasy use, and impulsivity, is complex, including likely contributions of impulsivity and risk-assessment decisions on the decision to initiate and continue Ecstasy use that make it difficult to assess causality.

6.0 Effects in Humans in Clinical Settings

6.1 History of Use in Clinical Settings

Shulgin and Nichols were the first to report on the effects of MDMA in humans [51]. In the 1970s, psychotherapists used MDMA-assisted psychotherapy to treat psychological disorders including anxiety [58]. Legal therapeutic use of MDMA continued until its placement on the U.S. list of Schedule I drugs in 1985 [57, 61, 307]. An estimated 500,000 doses of MDMA were administered during psychotherapy sessions in North America prior to its scheduling [49, 307]. A few uncontrolled human studies of MDMA

occurred in the 1980s [39, 54] including Greer and Tolbert's study of MDMA in a psychotherapeutic context.

Controlled human studies of MDMA commenced in the mid-1990s with a MAPS funded investigator-initiated Phase 1 dose-response safety study [43, 44]. Approximately 77 human trials with MDMA have been conducted globally over the past four decades outside the development program (N=1431) (see Appendix Table 1: Summary of Investigator-Initiated Trials with MDMA). MAPS also funded a Phase 2 investigator-initiated dose-response safety and efficacy pilot study in Spain that was terminated early due to political concerns. This study enrolled six participants, with four receiving a single session of MDMA-assisted psychotherapy without any safety concerns and some PTSD symptom reduction [81].

Based on past reports of MDMA use, nonclinical studies, and the results from these investigator-initiated trials with MDMA, the sponsor launched a Phase 2 Clinical Development Program in 2001 to develop MDMA-assisted psychotherapy for the treatment of chronic PTSD under a U.S. IND. Nine sponsor-supported Phase 2 studies of MDMA-assisted psychotherapy for PTSD have been conducted, and data from six has been published. The sponsor has initiated or plans to initiate several Phase 1 studies, at least one Phase 2 study and at least one Phase 3 study (see Table 2 for details of planned and ongoing studies.) These studies will include studies of MDMA pharmacokinetics, studies of MDMA-assisted psychotherapy in people with PTSD and a Phase 2 study of MDMA-assisted psychotherapy in people with eating disorders (see Table 5: Summary of Ongoing and Planned Sponsor-Supported Trials with MDMA).

Table 4: Summary of Completed Sponsor Supported Trials with MDMA

Study	NCT #	Location	Population	Therapy Teams (n)	MDMA Doses	Design	Exposed to MDMA at Any Dose[b]	Publications
PTSD								
MP-1	NCT00090064	Charleston, South Carolina	Crime, veterans	1	placebo (n=8), 125 mg (n=15)	Blinded RCT, open-label Stage 2	22	[3, 4]
MP-2	NCT00353938	Biberist, Switzerland	Various	1	25 mg (n=5), 125 mg (n=9)	Blinded RCT, open-label Stage 2 Open label Stage 3	14	[5]
MP-3	NCT00402298	Beer Yaakov, Israel	Various	1	25 mg (n=2), 125 mg (n=3)	Blinded RCT, planned Stage 2	5	Terminated early
MP-4	NCT01958593	Vancouver, Canada	Various	2	placebo (n=2), 125 mg (n=4)	Blinded RCT, open-label Stage 2	6	[1]
MP-8	NCT01211405	Charleston, South Carolina	Veterans, firefighters, police officers	1	30 mg (n=7), 75 mg (n=7), 125 mg (n=12)	Blinded RCT, open-label Stage 2	26	[2]
MP-9	NCT01689740	Be'er Ya'aqov, Israel	Various	5	25 mg (n=3), 125 mg (n=7)[a]	Blinded RCT, open-label Stage 2	10	[1]
MP-12	NCT01793610	Boulder, Colorado	Various	9	40 mg (n=6), 100 mg (n=9), 125 mg (n=13)	Blinded RCT, Open label Stage 2	28	[6]
MPVA-1	NCT02876172	Charleston, SC	Dyads w/one person w/ PTSD diag., one no PTSD	4	75 mg [1st session], 100 mg [2nd session]	Open label Phase1/Phase 2	12	[535]
MP16	NCT03282123	Multi-site; US, Israel	Various	33	80 mg; 100 mg	Open label	33	TBD
MP17	NCT03485287	Multi-site, Canada	Various	4	100 mg, 125 mg	Open label	4	TBD
Social anxiety								

MAA-1	NCT02008396	Los Angeles, CA	Adults on autism spectrum with social anxiety	1	placebo (n=4), 75-125 mg (8)	Blinded RCT, open-label arm	12	[536]
Illness/Anxiety								
MDA-1	NCT02427568	San Anselmo, CA	Anxiety related to life-threatening illness	3	125 mg (n=13) placebo (n=5)	Blinded RCT, Open Label Stage 2	18	[537]

*Completed Studies indicates that all subjects have completed the study. Clinical Study Reports are in progress.
Abbreviations: NCT=clinicaltrials.gov identifier; n=number of participants; m=months; w=weeks; TBD=To be determined
[a] The first two participants were open-label (125 mg MDMA) and were included in the efficacy analyses
[b] At treatment exit

Table 5: Summary of Ongoing and Planned Sponsor Supported Trials with MDMA

Study	NCT #	Location	Population	MDMA Doses	Design	Status/Publications
PTSD						
MP18	NCT04030169	Multi-site; Czech Republic, Netherlands, Norway, Portugal, UK	Various	80 mg (1st sessions), 80 or 120 mg (2nd, 3rd sessions)	Open label	Recruiting/ongoing, open-label
MAPP1	NCT03537014	Multi-site; US, Canada, Israel	Various	80 mg (1st sessions), 80 or 120 mg (2nd, 3rd sessions); placebo	Blinded RCT	Ongoing, blinded
MAPP2	NCT04077437	Multi-site; US, Canada, Israel		80 mg (1st sessions), 80 or 120 mg (2nd, 3rd sessions); placebo	Blinded RCT	Planned
MPVA6	TBD	Atlanta, GA	Various	120 mg	Open-label	Planned
MPVA5	TBD			TBD		Under development
MPGI	TBD			TBD		Under development
EAMP1	TBD	Multiple sites	Various	80 mg (1st sessions), 80 or 120 mg (2nd, 3rd sessions)	Expanded Access; open-label	Planned
Eating Disorders						
MED1	NCT04454684	Multi-site; Montreal, PQ, Vancouver, BC; (Canada), Denver, CO (US)	Anorexia nervosa; binge eating disorder	80 mg	Open-label, not randomized	Planned
Healthy Controls						
MT-1	NCT01404754	Charleston, SC; Boulder, CO; Santa Fe, NM	Candidate trainees in MDMA-assisted Psychotherapy	placebo, 125 mg	WS, full crossover RCT	Ongoing, blinded
MT-2	NCT04073433	Multi-site	Trainees in MDMA-assisted psychotherapy	120 mg	Open-label	Planned

MPVA-4	NCT03181763	Atlanta, GA.	Healthy, aged 21-55, prev. experience w/MDMA	placebo, 100 mg MDMA	Between-subjects RCT	Ongoing, blinded
MPKH	NCT03606538	San Francisco, CA	Healthy controls and participants with moderately impaired liver function	80 mg	Open label	Planned/initiate, none enrolled
MPKF	TBD	San Francisco, CA	Healthy controls	120 mg	Open label crossover (with/without fasting)	Under development

Abbreviations: NCT=clinicaltrials.gov identifier

6.1.1 Phase 1 Studies

The sponsor is conducting two ongoing Phase 1 studies, MPVA-4 and MT-1. MPVA-4 is a Phase 1, randomized, placebo-controlled, double-blinded between-groups study in approximately 30 healthy participants examining the effects of MDMA on presence and intensity of startle response after receiving cues that were previously related to a startling stimulus. People will receive 100 mg MDMA or placebo and undergo another startle-related task with the same cues, but without the same stimuli. In study MT-1, healthy volunteers who have had completed training in manualized MDMA-assisted psychotherapy undergo two sessions in a within-subject, double-blind crossover study, receiving placebo during one session and 125 mg MDMA during the other. Subjective effects, mood, and reactions are also being assessed in the ongoing Phase 1 placebo-controlled study of MDMA-assisted psychotherapy, in healthy volunteers who have completed training in manualized MDMA-assisted psychotherapy (MT-1).

6.1.2 Phase 2 Studies

Most data reported are from Phase 2 studies of MDMA-assisted psychotherapy for PTSD. Data from a pair of investigations of MDMA-assisted psychotherapy for other indications are also presented. Studies have employed a range of comparator and active doses, from an initial dose of 25 mg to 150 mg MDMA. The lowest dose in use has been 25 mg, used as a placebo or low dose comparator in studies MP-2 and MP-9. Typically, Stage 1 was blinded and Stage 2 was open-label in which participants who received placebo or comparator doses in Stage 1 received active MDMA. The highest dose (150 mg) was offered to a limited number of participants in MP-2 as part of "Stage 3," an open-label arm for non-responders in Stage 1 and/or Stage 2. All studies have employed 125 mg usually followed 1.5 to 2 hours later by a supplemental dose of 62.5 mg MDMA as the primary active treatment. The supplemental dose given at approximately peak exposure from the initial dose does not significantly impact intensity of pharmacodynamic effects, but does enable a longer period to process trauma in the context of dosing sessions. In sponsor-supported studies, MDMA or placebo/comparator is administered after preparatory psychotherapy during two or three 8-hour Experimental Sessions scheduled 2 to 5 weeks apart, each followed by at least three sessions of integrative psychotherapy. This treatment model is based on historical experience with MDMA use as an adjunct to psychotherapy. See Table 4 for more details on completed studies and Table 5 on planned and ongoing studies.

MAPS has completed six blinded randomized, controlled Phase 2 investigations of MDMA-assisted psychotherapy with one extension study [1]. These studies explored the reproducibility of treatment outcomes of MDMA-assisted psychotherapy in people with chronic PTSD that failed to respond to at least one course of psychotherapy or at least one course of pharmacotherapy. Phase 2 studies MP-8 and MP12 (legacy studies that have been converted to current data standards for CDISC submission), along with the Phase 2 lead-in study MP-16 are highlighted below as the sponsor plans to include these studies to support the safety database in this NDA with the FDA. The three smaller Phase 2 studies (MP-4, MP-8, and MP-17) are summarized below, but due to their size and design differences from the Phase 3 studies, they are not planned for inclusion in the NDA submission.

6.1.2.1 Study MP-8

Study MP-8 (N=26) compared 3 doses of MDMA (30 mg, 75 mg, or 125 mg initial dose, with an optional supplemental dose equivalent to half the initial dose) in military veterans, firefighters, and police officers ("first responders") with service-related PTSD, with an average age of 37.2±10.3 years. Each dosing arm participated in two blinded Experimental Sessions with the assigned dose, followed by open-label crossover (three open-label sessions consisting of a full active dose of 100 or 125 mg initial dose, with an optional supplemental dose equivalent to half the initial dose). These study results were published in 2018 [2]. This study found that the decreases in Clinician Administered PTSD Scale (CAPS-IV) PTSD symptom severity, expressed as mean (SD) at the Primary Endpoint, in the 75 mg (-58.3 (9.8)) and 125 mg groups (-44.3 (28.7)), had significantly decreased (p=0·001) compared to the 30 mg group (-11.4 (12.7)) [2].

There was one SAR that occurred in this study: subject 0811 experienced an increase in frequency of ventricular extrasystoles, a form of cardiac arrhythmia, on the day of his third and final Experimental Session with open-label 125 mg MDMA. For further detail see Section 6.4.1.4 Serious Adverse Reactions. Detailed safety information from this study is included in Section 6.4 Safety of MDMA in Humans.

6.1.2.2 Study MP-12

Study MP-12 (N=28) compared 3 doses of MDMA (40 mg, 100 mg, or 125 mg initial dose of MDMA, with an optional supplemental dose equivalent to half the initial dose) in participants with PTSD from any cause, with an average age of 42.0±12.9 years. Each dosing arm participated in two blinded Experimental Sessions with the assigned dose, followed by open-label crossover (three open-label sessions in the low dose arm or one open-label session in the other two active dose arms consisting of a full active dose of 100 or 125 mg initial dose, with an optional supplemental dose equivalent to half the initial dose). These study results were published in 2018 [6]. This study found that in the intent-to-treat set, the CAPS-IV PTSD symptom severity score reduction, expressed as mean (SD), at the Primary Endpoint were -26.3 (29.5) for 125 mg, -24.4 (24.2) for 100 mg, and -11.5 (21.2) for 40 mg, though a statistically significant reduction (p=0.03) was only demonstrated in the per protocol set for the 125 mg dose compared to the 40 mg dose [6]. Detailed safety information from this study is included in Section 6.4 Safety of MDMA in Humans.

6.1.2.3 Study MP16

Study MP-16 (N=33) was conducted as a multi-site Phase 2 open-label study of MDMA-assisted psychotherapy for PTSD. MDMA (80 mg or 120 mg with an optional supplemental dose equal to half of the initial dose) is administered in three psychotherapy sessions with non-drug preparatory and Integrative Sessions. An aim of this was to provide supervision to newly trained therapy teams prior to participating in the Phase 3 trials. Thirty-seven participants completed these studies. In this study, we began a sub-study to pilot participants returning home following Experimental Sessions with MDMA-

assisted psychotherapy without having a post-visit overnight stay in the PTSD population. This study is undergoing final data review.

6.1.2.4 Other Phase 2 Studies

The sponsor has also completed three international Phase 2 studies. Study MP-4 (N=6), conducted in Canada, compared placebo to 125 mg initial dose of MDMA, with an optional supplemental dose equivalent to half the initial dose, in participants with an average age of 47.7±6.0 years. Study MP-9 (N=10), conducted in Israel, compared an initial dose of 25 mg to 125 mg MDMA, with an optional supplemental dose equivalent to half the initial dose, in participants with an average age of 36.7±8.0 years. Study MP-17 (N=4), a parallel Canadian study to the U.S. MP-16 study described above, was conducted as a two-site Phase 2 open-label study of MDMA-assisted psychotherapy for PTSD. MDMA (100 mg or 125 mg with an optional supplemental dose equal to half of the initial dose) was administered in three psychotherapy sessions with non-drug preparatory and Integrative Sessions. Similar to MP-16, one aim of this study was to provide supervision to newly trained therapy teams prior to participating in the Phase 3 trials.

The sponsor has additionally completed an open-label study of a combination of MDMA-assisted psychotherapy and cognitive behavioral conjoint therapy in six dyads that include a participant with PTSD and a participant without PTSD, and relationship distress (MPVA-1, N=12).

6.1.3 Phase 3 Studies

Studies MAPP1 and MAPP2 are two Phase 3 studies being conducted as pivotal trials to support an NDA with the FDA for approval of MDMA-assisted psychotherapy to treat PTSD. These multi-site trials are planned to randomize participants (n=approximately 100/trial) in a 1:1 ratio to receive MDMA or inactive placebo during 3 psychotherapy sessions, with 3 Integrative Sessions following each Experimental Session. The dosing regimen is 80 mg for the first session and an optional titration dose of 120 mg during the second and third sessions. An optional supplemental dose equal to half the initial dose is available during each session. MAPP1 began enrollment in November 2018 and MAPP2 is scheduled to begin enrollment in 2020.These studies will continue the sub-study that began in MP-16 to pilot participants returning home following Experimental Sessions with MDMA-assisted psychotherapy (and not having a post-visit overnight stay) in the PTSD population.

6.1.4 Non-PTSD Indication Phase 2 Studies

The sponsor has completed one Phase 2, placebo-controlled, double-blind study of MDMA-assisted psychotherapy in autistic adults with social anxiety (MAA-1, N=12) and one study of MDMA-assisted psychotherapy in people experiencing anxiety in the face of a life-threatening illness (MDA-1, N=18). Findings from the first study have been published, and findings from the second study have been submitted for publication.

The sponsor is planning to initiate a study of MDMA-assisted psychotherapy in people with eating disorders (MED-1). It will take place at two sites in Canada, and one in the US, and will enroll 12 people with anorexia nervosa and six with binge eating disorder.

6.2 Pharmacology in Humans

The effects in humans presented in the sections below will include findings from both sponsor-supported clinical trials in patient populations as well as studies conducted in controlled laboratory settings in healthy volunteers without sponsor support. Findings from extensive human research being conducted on the pharmacology and mechanism of action will be presented in addition to the information required by FDA in order to support the safety profile of MDMA.

Common AEs of MDMA reported in non-sponsor supported Phase 1 studies in healthy volunteers include elevation in blood pressure and heart rate, increased anxiety or dysphoria, and dilated pupils [18-21]. Some reports indicated decreased rather than increased alertness [18]. Other common AEs reported in controlled studies of MDMA include reduced appetite, dizziness, tight jaw, bruxism (tooth-grinding), disturbance in attention, impaired gait or balance, dry mouth, and thirst. Participants in some studies also reported or exhibited changes in cognition, such as increases in speed of thought or thought blocking, facilitated imagination or recall [23], and unusual thoughts or ideas [20]. Other less commonly reported events include paraesthesia (unusual body sensations) such as tingling, or feeling hot or cold. MDMA can produce anxiety in healthy volunteers [20, 21, 23]. These effects are transient and dissipate as drug effects wane. One study found that women were more likely to report these events than men [21], while another study failed to support gender differences in reporting AEs [538].

The sponsor will conduct pharmacokinetic studies in humans to assess the effects of moderate hepatic impairment and effects of food or diet on MDMA metabolism concurrent with Phase 3 trials for treatment of PTSD. The following description of pharmacodynamics or pharmacokinetics of MDMA are from available published literature. Beginning in the early to mid-1990s, several research teams conducted studies of the pharmacodynamics and pharmacokinetics of MDMA [21, 24, 28, 83, 248, 259, 539-541] without receiving sponsor support.

6.2.1 Pharmacokinetics and Product Metabolism in Humans

The maximum proposed clinical dosing regimen consists of three divided single-dose exposures to racemic MDMA spaced approximately a month apart with a 80 mg or 120 mg initial dose followed by a 40 mg or 60 mg supplemental half-dose, administered 1.5 to 2 hours after initial dose at C_{max}. Mean (%CV) C_{max} and AUC at 125 mg MDMA [542] is 223.5±38.5 ng/mL (N=136) and mean AUC: 948±172.9 ng*h/mL (N=136). The clinical dosing regimen does not reach steady state, as the intended usage is up to 3 exposures to single-dose with at least 2 weeks washout between doses.

Onset of MDMA effects occurs 30 to 60 minutes after oral administration of 75 to 125 mg [18, 19], peak effects appear 75 to 120 minutes post-drug [17, 20-22], and duration of effects lasts from 3 to 6 hours [20, 21, 23] with most effects returning to baseline or near-

baseline levels 6 hours after final drug administration. Self-reported duration of effects may increase as the dose of MDMA increases [17]. Administering a second dose of MDMA 2 hours after the initial dose, twice that of the initial dose, does not significantly extend the duration of measurable physiological or subjective effects [260]. Orally administered MDMA has a half-life of 7 to 8 hours in humans and half-life is marginally extended if an additional dose is administered 2 hours after an initial dose [260]. MDMA and its metabolites have been found in oral fluid samples at much higher concentrations than in plasma, for 24 to 48 hours for the former and 12 to 47 hours for the latter after oral administration of 1 to 1.6 mg/kg MDMA [543].

6.2.1.1 Absorption

MDMA has not been studied in humans with i.v. administration. As such, absolute or relative bioavailability is unknown. At a dose of 75 mg, MDMA is rapidly absorbed in humans, with an observed Tmax of 1.8±0.4 hours by the oral route. At higher oral doses of 125 mg a slightly longer Tmax 2.4±1.0 hours was observed [24].

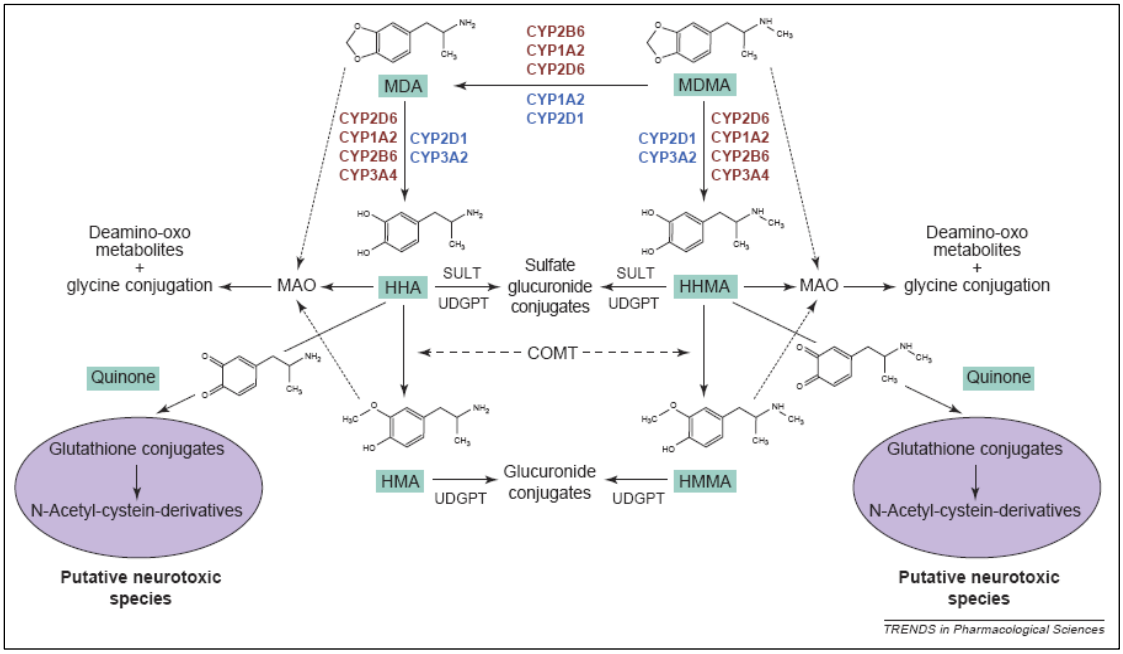
6.2.1.2 Distribution

MDMA has been shown to be partially bound to plasma proteins in humans. The mean unbound fraction of MDMA in plasma was measured in humans to be 34 to 40% at therapeutically active doses (1 to 1.6 mg/kg) [248]. The volume of distribution of MDMA at 1 mg/kg was observed to be 5.5±1.1 L/kg (dose range based on weight 43 mg-106 mg) in humans [248]. The volume of distribution of MDMA at 1.6 mg/kg was observed to be 5.5±1.3 L/kg (dose range based on weight 69 mg-150 mg) in humans [248].

6.2.1.3 Metabolism

MDMA metabolism in the liver is saturable in a dose-dependent manner and follows non-linear pharmacokinetics. MDMA is metabolized by N-demethylation to the only active metabolite MDA by several enzymes, including CYP2D6 (>30%), CYP1A2, CYP3A4, CYP2C19, and CYP2B6, followed by COMT. The parent compound and MDA are further O-demethylated to HHMA and HHA, respectively. Both HHMA and HHA are subsequently O-methylated mainly to HMMA and HMA. These four metabolites, particularly HMMA and HMA, are excreted in the urine as conjugated glucuronide or sulfate metabolites. Metabolites of MDMA are summarized in Figure 2 [544-549].

Figure 2: Metabolism of MDMA in Humans



Metabolism of MDMA in humans (in red) compared to metabolism in rats (in blue). Reproduced with permission of R. de la Torre [247].

It is likely that active doses of MDMA inhibit CYP2D6 function, as measured by examining the effects of MDMA on dextromethorphan metabolism. Inhibition of CYP2D6 by MDMA was demonstrated first in a physiological model derived from data collected after oral administration in humans [550]. O'Mathuna and colleagues present evidence that CYP2D6 activity may not fully recover until 10 days after MDMA [551, 552]. 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 [259]. MDMA may produce increased activity of the enzyme CYP1A2, as evidenced by comparing caffeine metabolism before and after MDMA [553]. Findings support the enantioselective nonlinear metabolism of MDMA and its metabolites measured in blood and urine [554-556]. CYP2D6 may be involved in stereoselective metabolism of MDMA, but to a clinically insignificant degree [556].

Comparison of pharmacokinetic-pharmacodynamic relationships for MDMA reveals acute pharmacodynamic tolerance. Despite 8 hours of half-life of MDMA, and persistent high drug levels in the blood, most pharmacodynamic effects of the initial dose rapidly return to baseline within 4 to 6 hours [541]. 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, a dose regimen similar but not identical to timing between the initial and supplemental dose of MDMA in sponsor-supported trials, reported higher peak plasma MDMA than might be expected and lower levels of the MDMA metabolites HMMA and HMA [260]. The initial dose appears to saturate or inhibit the metabolic pathway mediated by CYP2D6, leading a supplemental dose to form metabolites at a lower rate than expected and

increasing exposure to the parent drug (see Figure 2). A study comparing the effects of a single 100 mg dose with an initial administration of 50 mg followed two hours later by 100 mg reported plasma MDMA concentrations increased by more than expected based on dose proportionality, C_{max} +12.8% and AUC +16.2%. inactive metabolite HMMA concentration decreasing in plasma by C_{max} -38.2% and AUC -29.8%, which was more than what would be expected based on dose proportionality. These findings are further supported by examining plasma MDMA after two doses of 100 mg given four hours apart [557], plasma MDMA concentrations increased C_{max} +23.1% and AUC +17.1%, and active metabolite MDA concentration increased in plasma by C_{max} +14.2% and AUC +10.3%, which was also more than would be expected based on dose proportionality, likely due to metabolic autoinhibition of CYP2D6. These findings suggest that intensity of most subjective and physiological effects of MDMA would not be significantly impacted by the supplemental doses in sponsor-supported studies due to acute tolerance to its prototypical effects [557].

This acute tolerance could be caused by functional depletion of stored serotonin that prevent further release despite MDMA still being present [541], or are a result of MDMA transport into intracellular spaces is saturable due to limited transport capacity [102]. Additionally, reversible inhibition of tryptophan hydroxylase as observed in rodents [257], or internalization of serotonin reuptake transporters from the plasma membrane leading to less serotonin release [77], would support self-limiting effects of MDMA. On the other hand, although SERT can be internalized, the evidence suggests that accumulation of extracellular serotonin stimulated by MDMA affects SERT trafficking by perpetuating cell-surface SERT expression, but in contrast promotes internalization of DAT and NET [102, 558].

6.2.1.4 Elimination

Although the hepatic route is thought to be the major route of metabolism in humans with 50% to 75% of the parent compound being metabolized, renal clearance accounts for 8% to 11% of elimination of MDMA and its metabolites. After 1.0 mg/kg MDMA, the majority was excreted in urine as the inactive metabolites HMMA sulfate (13%), followed by DHMA 3-sulfate (9%), and HMMA glucuronide (5%), and only 8% as the parent compound MDMA [248]. After 1.6 mg/kg MDMA, the majority was excreted in urine as the inactive metabolites HMMA sulfate (10%), followed by DHMA 3-sulfate (9%), and HMMA glucuronide (4%), and only 11% as the parent compound MDMA. Studies examining metabolism of 100 mg MDMA reported similar excretion values [248, 559-563].

Metabolites are primarily excreted as glucuronide and sulfate conjugates [546, 564, 565] with some evidence for stereoselective metabolism of the glucuronide and sulfate metabolites [564]. Urinary excretion of the metabolite HHMA after 100 mg MDMA in four men was 91.8±23.8 mol and 17.7% recovery [563]. By contrast, urinary recovery of the major metabolite HMMA after 100 mg was 40% [566]. Urinary recovery for MDMA and MDA were higher when a second dose of 100 mg MDMA was administered 24 hours after an initial dose of 100 mg MDMA when compared with a single dose [559]. 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 [567].

Renal clearance (CL) by dose of MDMA administered were 12.8±5.6 L/h at 75 mg, 20.4 -12.3 L/h at 100 mg, 13.0±5.4 L/h at 125 mg, and 5.2-11.3 L/h at 150 mg [24]. Oral clearance (CL/F) by dose of MDMA administered was 0.62±0.19 L/h/kg at 1.0 mg/kg (dose range by weight 43 mg-106 mg) and 0.48±0.11 L/h/kg at 1.6 mg/kg (dose range by weight 69 mg-150 mg) [248].

To date, there are no known clinical trials quantifying excretion of MDMA into breastmilk in humans.

6.2.1.5 Pharmacogenomics

The effects of variation in genotypes for the enzymes CYP2C19, CYP2B6, and CYP1A2 on metabolism of 75 and 125 mg MDMA in a pooled sample of 139 participants found that variants with less functional versions of CYP2C19 and CYP2B6 exhibited +15% C_{max} for MDMA, +50% C_{max} of MDA, and -50 to 70% C_{max} of HMMA. Two participants with the poor metabolizer variants of CYP2C19 had greater cardiovascular response to MDMA, and tobacco smokers with inducible CYP1A2 exhibited higher conversion of MDMA to MDA [568]. These results demonstrate compensatory mechanisms that involve contributions from multiple enzymes when CYP2D6 is inhibited through a metabolic complex with MDMA. A pair of in vitro studies modeling metabolism in human liver cells and insect cells reported that CYP2D6 may have functional heterogeneity, or variation in response to substrates, and that less than 50% of CYP2D6 may be inhibited by MDMA, and concluded that the ability of MDMA to inhibit CYP2D6 may be overestimated [569]. The in vitro models seem at odds with lingering reduction in activity detected in humans.

The enzyme COMT and monoamine oxidase may also be involved in the metabolism of MDMA [566]. At least one variation in COMT genotype may affect MDMA elimination rate (Ke) and systolic blood pressure (SBP) after MDMA [570]. As a monoamine reuptake inhibitor that leads to monoamine release and inhibits monoamine oxidase-A [107], combining MDMA with a monoamine oxidase inhibitor (MAOI) medication presents a risk for provoking serotonin syndrome and increases in sympathetic activity. Fatalities have occurred apparently as a result of combining MAOI medications with MDMA [108, 109]. For this reason, MAOI medications are tapered for at least five half-lives of the medication and active metabolites, plus 1 week for symptom stabilization in sponsor-supported studies.

An examination of subjective, physiological, and pharmacokinetic effects of variations in genes tied to the serotonin system in a sample of 124 participants sought to investigate differences in plasma levels after 125 mg MDMA [571]. While they detected a slight increase in cumulative MDMA levels (AUC) in one variant of the 5-HT1A receptor and very slight decrease in C_{max} MDMA levels in variant of the 5HT1B receptor, neither effect was found to be significant after correcting for number of tests.
Variations in genes related to serotonin synthesis and three serotonin receptors (5HT1A, 5HT1B, and 5HT2A), and SERT made very little difference in vital signs or subjective effects of 125 mg MDMA in a study in 124 healthy controls [571]. Gene variants in the 5HT2A receptor, SERT, and tryptophan hydroxylase-1 influenced subjective effects, but

these effects were no longer significant after correcting for number of tests. Pooled analyses of a sample of 132 healthy participants who received 125 mg MDMA in placebo-controlled studies reported that variation in an oxytocin receptor gene (rs1042778TT) reported greater feelings of trust after MDMA, but that variations in oxytocin receptor genes did not affect cognitive or emotional empathy [572].

6.2.1.6 Pharmacokinetic Drug Interactions

Co-administration studies with MDMA after pre-treatment with CYP2D6 inhibiting prescription drugs paroxetine [573] and bupropion [574] have been completed. In addition, drug interaction studies with methylphenidate [541] and dextromethorphan [552] have been completed. MDMA reversibly inhibits CYP2D6 and decreases CYP3A4 activity, with CYP2D6 function normalizing after 10 days. MDMA increases CYP1A2 activity, as measured by caffeine challenge, by 20% to 40% when CYP2D6 is saturated or inhibited [552]. Due to known MDMA effects of CYP2D6 inhibition, drug interaction studies with CYP2D6 inhibitors are presented in detail below. For additional pharmacokinetic parameters from drug interaction studies, please refer to Appendix Table 22: Highlights of MDMA Clinical Pharmacology and Cardiac Safety.

Paroxetine is an SSRI approved for PTSD and patients interested in MDMA-assisted psychotherapy are likely to be on maintenance treatment with this drug. In a randomized, double-blind, crossover, placebo-controlled trial in healthy male volunteers who were CYP2D6 extensive metabolizers (N=7), paroxetine given for 3 days before MDMA resulted in significant increases of MDMA area under the plasma concentration-time curve from 0 to 27 hours (AUC_{27}) by +23%, AUC from zero to infinity (AUC_{∞}) by +27% and maximum plasma concentration (C_{max}) by +17%, without significant differences in MDMA T_{max} [573]. MDMA elimination-related pharmacokinetic parameters showed a significant reduction of plasma clearance by -29%, renal clearance by -19%, and hepatic clearance by -32%. Elimination half-life extended from 8.3 to 9.9 hours. A 21% decrease in C_{max} of HHMA which is an MDMA metabolite, with no significant differences in AUC_{27}, AUC_{∞}, K_e and elimination half-life were found. HMMA showed a decrease in plasma concentrations with a reduction in AUC_{27} of -28%, AUC_{∞} of -20% and C_{max} of -46%. The active metabolite MDA, which is produced in the minor metabolic pathway, was shown to have an increase in C_{max} of +17% and AUC_{27} +16%. Following paroxetine pretreatment, the urinary recovery (0-45 hours) of the parent compound MDMA increased by 11%; HHMA and HMMA urinary recoveries were 27% and 16% lower, respectively, compared to placebo. The ratio of C_{max} values of paroxetine and its metabolite on Days 1 and 3 showed a threefold reduction, with no differences in T_{max}. As these elevations were not clinically meaningful, the sponsor concludes that drug interactions with previously approved PTSD medications that are also CYP2D6 inhibitors, such as paroxetine, would be suitable from a safety standpoint for co-administration with MDMA, although some subjective MDMA-induced effects may be reverted or attenuated [573].

As MDMA is a monoamine reuptake inhibitor that leads to monoamine release and inhibits monoamine oxidase-A [107], combining MDMA with a MAOI medication may present a risk for provoking serotonin syndrome and increases in sympathetic activity, as reported in four deaths associated with concomitant use of MDMA and the MAOi

moclobemide [108]. However, a recent in vitro study examining the IC50 of MDMA and MDA against serotonin (24.7 micrometer (µM) and >8.5 µM, respectively) and dopamine (19.2 µM and >8.4 µM, respectively) concluded that inhibitory potential (<20%) was unlikely to be relevant at plasma values observed in humans, which are estimated to be in the range of 1µM [575]. Nevertheless, the sponsor requests a waiver of an in vivo interaction study to avoid potential pharmacodynamic interactions based on published case reports.

Bupropion is a norepinephrine dopamine reuptake inhibitor approved for treatment of major depression and smoking cessation, and patients interested in MDMA-assisted psychotherapy may be on maintenance treatment with this drug. Bupropion inhibits CYP2D6 and also competitively inhibits CYP2B6, which metabolizes bupropion to hydroxybupropion. 125 mg MDMA was administered after 1 week of bupropion pre-treatment in a double-blind, placebo-controlled, crossover study in 16 healthy volunteers, in CYP2D6 extensive metabolizers (N=13) and intermediate metabolizers (N=3). Bupropion pretreatment increased the C_{max} of MDMA by +14% ($p<0.01$), AUC_{24} by +33% ($p<0.001$), and prolonged its t1/2 by +24% ($p<0.01$). In contrast, bupropion pretreatment decreased the C_{max} of MDA by -15% ($p<0.01$), and decreased AUC_{24} by -12% but this failed to reach significance [574]. When results were re-analyzed with stereoselective methods [556], bupropion pre-treatment increased the C_{max} of R-MDMA by +9% and the AUC from 0 to 24 hours (AUC_{24}) by +25%. Bupropion pre-treatment increased the C_{max} of S-MDMA by +16% and the AUC_{24} by +38%. In contrast, bupropion pre-treatment decreased the C_{max} of R-MDA by -27% and the AUC24 by -26%, and the C_{max} of S-MDA by -24% and the AUC_{24} by -20%. Bupropion pre-treatment decreased the C_{max} and the AUC_{24} of CYP2D6-dependent inactive metabolite stereoisomers by approximately -40%. The changes that were observed in the intermediate metabolizers were comparable to the extensive metabolizers, although the intermediate metabolizer sample was small (N=3). Although changes in stereoselectivity based on CYP2D6 activity were observed, these are unlikely to have clinical relevance. Bupropion and hydroxybupropion stereoisomer kinetics were unaltered by MDMA co-administration. As these elevations were not clinically concerning, the sponsor concludes that drug interactions with non-serotonergic medications that are also CYP2D6 inhibitors, such as bupropion, would be suitable from a safety standpoint for co-administration with MDMA.

6.2.2 Pharmacodynamics

6.2.2.1 Primary Pharmacodynamics

MDMA promotes release and inhibits reuptake of monoamine neurotransmitters, and directly binds or indirectly activates downstream receptors, with actions on the serotonin system likely responsible for most of its subjective and physiological effects in humans. MDMA is associated with changes in several neurohormones as well with some of these actions likely responsible for some changes in subjective and physiological effects.

Estimates from animal data suggest the LD50 in humans is probably between 10 to 20 mg/kg [16]. 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 individuals. The pharmacokinetics of MDMA in humans have been characterized in blood and urine samples using oral doses of up to 150 mg MDMA [24]. MDMA is a triple monoamine reuptake inhibitor and similar drugs in this class have been found to exert potent anti-depressant activity with a potentially favorable safety profile [25, 26]. MDMA concomitantly promotes release, inhibits reuptake, and extends duration of serotonin, norepinephrine, and dopamine in the synaptic cleft to increase serotonergic, noradrenergic, and dopaminergic neurotransmission. MDMA has self-limiting subjective and physiological effects as previously described.

In addition to neuroendocrine and norepinephrine-mediated effects, MDMA may target similar binding sites on the SERT, as do already approved PTSD medications Paxil and Zoloft, which are both Selective Serotonin Reuptake Inhibitors (SSRIs). Like the SSRI Prozac, MDMA also inhibits MAO-A to extend presence of serotonin in the synaptic cleft [107]. Pre-treatment or co-administration studies of SSRIs with MDMA suggest that this combination is safe within controlled settings and that it attenuates most effects of MDMA. SSRIs appear to attenuate or eliminate most subjective, physiological and immunological effects of MDMA likely due to competition for binding sites on the SERT, which may prevent transporter-mediated serotonin release [84, 576-579] (see Appendix Table 1: Summary of Investigator-Initiated Trials with MDMA). Additional effects of each SSRI beyond reuptake inhibition on production, release, and degradation of serotonin are likely responsible for variations between SSRI co-administration findings.

The role of serotonin release on the potentially therapeutic effects of MDMA-assisted psychotherapy has yet to be investigated, however reduced feelings of sociability and closeness to others after paroxetine pre-administration suggests that serotonin release is at least partially involved in prosocial effects that are thought to be therapeutically relevant [84]. These subjective effects are predominately mediated by direct or indirect action on 5HT2A receptors [86, 186, 580] with at least one study concluding that the effects of MDMA upon positive mood are at least due in part to 5HT2A receptor activation [86]. Findings suggest that the 5HT1A receptor was partially involved in producing the subjective effects of MDMA [86, 184-186]. A study using receptor-enriched brain mapping of functional connectivity (described in more detail below) reported that changes in functional connectivity in 5HT2A-receptor enriched maps were associated with increased reports of having a spiritual experience [581].

Human MDMA studies suggest that norepinephrine release also contributes to the pharmacodynamic, physiological, and psychological effects of MDMA [221, 222, 224, 582, 583], with noradrenergic antagonists attenuating MDMA effects on blood pressure and mood (see Appendix Table 1: Summary of Investigator-Initiated Trials with MDMA).

Most of the psychostimulant-like and prosocial or 'entactogenic' subjective effects of MDMA are blocked after administration of the dual selective serotonin and norepinephrine uptake inhibitor (SNRI) duloxetine [224, 583], and that these effects may relate to changes in neurohormones such as oxytocin and copeptin. [583, 584]. As the NET unexpectedly has a greater affinity than the DAT for dopamine, it preferentially

clears dopamine in brain areas where there is a greater concentration of NET, such as the frontal cortex [585].

Some MDMA effects on human mood and anxiety may be attributed to dopamine release based on the finding that pretreatment with haloperidol, a dopamine receptor antagonist with partial selectivity for the D2 receptor subtype, diminished MDMA-induced positive mood and increased anxiety, though haloperidol alone was associated with dysphoria [586]. Studies comparing MDMA with the dopaminergic and adrenergic drug methylphenidate and bupropion suggest that dopamine release and inhibition of uptake play a minor role, if any, in producing the effects of MDMA [587]. MDMA, but not methylphenidate, increased trust, openness, and closeness to others, and bupropion prolonged the course of subjective effects without reducing or enhancing them [574].

6.2.2.2 Secondary Pharmacodynamics

MDMA produces a robust increase in the neurohormone oxytocin, a neurohormone associated with trust and affiliation, [83, 588-590], a finding first seen in a naturalistic study that reported elevated levels of oxytocin in clubgoers with detectable blood MDMA levels when compared to clubgoers without detectable levels of MDMA [454], and confirmed in blinded placebo-controlled experiments [83]. However, studies comparing increases in empathy or prosocial effects of MDMA with intranasal oxytocin have failed to find indications that the two substances produce similar effects with MDMA producing greater feelings of sociability and emotional empathy than oxytocin [56, 591]. Using pindolol to block 5-HT1A receptor mediation of oxytocin's effects, Kuypers and colleagues determined that MDMA increased emotional empathy while oxytocin did not produce similar effects on measures of empathy and social interaction [591]. Pooled data across six placebo-controlled within-subjects' studies in 118 participants confirmed an increase in emotional empathy without an increase in cognitive empathy [590]. However, interpretation of these results were limited because Kuypers and colleagues [590, 591] did not measure within-subject correlation of subjective effects with multiple post-MDMA oxytocin levels, as was done by Dumont and colleagues in their clinical trial showing a positive within-subject correlation after MDMA for oxytocin and prosocial effects [83].

MDMA acutely increases cortisol, prolactin, and adrenocorticotropic hormone concentrations in a dose dependent manner [19, 20, 44, 55, 85, 223, 559, 592-595], whereas growth hormone levels are unchanged by up to 125 mg MDMA [19]. A crossover study comparing the effects of MDMA and methylphenidate found that MDMA increased serum cortisol while methylphenidate did not [595]. Increases in cortisol and prolactin peak at about 2 hours after MDMA administration [19, 44]. A second dose of 100 mg MDMA, given 4 hours after an initial 100 mg, produces a second increase in cortisol during an interval when cortisol levels are declining [596], and a dose of 100 mg MDMA, given 24 hours after an initial dose, stimulates a greater release of cortisol but not prolactin [559]. Doses of 0.5 and 1.5 mg/kg MDMA elevated cortisol, and under stressful versus less stressful conditions [597].

MDMA may affect levels of other hormones. 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 [20]. These findings suggest a relationship between serotonin release and increased serum cortisol. Two studies have found that MDMA increased AVP [231, 583]. Neither study reported analysis or findings concerning any relationship between AVP levels and the subjective, emotional or social effects of MDMA.

A study applying a high-throughput detection method using liquid chromatography/mass spectrometry to assess changes in chemical markers (the "metabolome"), after 100 mg MDMA in 16 healthy volunteers, and detected elevation in cortisol, pregnenolone, and calcitriol, a metabolite of vitamin D after MDMA 4 hours after MDMA [592]. Boxler and colleagues detected a comparable increase of several factors (hydroxyeicosatetraenoic acid, dihydroxyeicosatetraenoic acid, and octadecadienoic acid) associated with mediating inflammation, and that the authors interpreted as signs of an inflammatory process.

A study applying receptor-enriched mapping and functional connectivity in a sample of 20 men reported that 100 mg MDMA activated brain areas assumed to have high 5HT1A density or high levels of SERT density. Despite failing to find a significant change in functional connectivity after MDMA in brain regions high in 5HT2A receptors, Dipasquale and colleagues reported that activity seen in these areas after MDMA were associated with reporting a spiritual experience [581]. This investigation also found a relationship between time course of MDMA effects and changes in functional connectivity in brain areas associated with 5HT1A receptor density, and reported decreased functional connectivity in several cortical areas, including specific areas of the temporal and frontal cortex, and insula, acutely after MDMA. Another investigation of functional connectivity after administering 100 mg to healthy volunteers reported decreased network connectivity in the right insula/salience network [598] with decreased connectivity associated with changes in subjective ratings of trait anxiety and bodily sensations.

6.2.3 Physiological Effects

6.2.3.1 Central Nervous System

Early investigations of MDMA in healthy volunteers with PET detected decreased left amygdalar activity and increased frontal activity [599]. Subsequent studies in healthy volunteers have found signs of reduced activity in R amygdala and hippocampus, a decrease in medial prefrontal cortex coupling with the hippocampus, and reduced right insular/salience network connectivity [598] (see Appendix Table 1: Summary of Investigator-Initiated Trials with MDMA). Decreased activity in the amygdala may be indicative of reduced reactions to potential threats [600]. MDMA (100 mg) increased subjective ratings of positive mood in response to positive memories and decreased negative response to negative memories. Attenuated activity in the left anterior temporal area was detected after MDMA during worst memory recall [32].

During a task that required keeping a visual target cue in mind, visual attention, and response inhibition, brain imaging detected changes in parietal activity after 75 mg

MDMA but not with placebo [601]. MDMA increased activity in frontal areas and decreased activity in occipital sites as measured via functional MRI (fMRI) [602]. Reduced resting-state cerebral blood flow (CBF) in right amygdala and hippocampus after MDMA was associated with greater intensity of self-reported subjective effects [603]. Participants given MDMA exhibited similar brain activity when reading or encoding a word list, which suggests that they were investing similar effort into both tasks.

Behavioral Effects

MDMA increases positive mood and anxiety [18, 20-22] on measures of alteration in consciousness and subjective effects. People receiving active doses of MDMA defined as 75 to 125 mg, experience euphoria, positive mood, vigor, and positively experienced derealization, consonant with early retrospective reports, but also report experiencing anxiety, tension, and dysphoria, as well as concern over losing control over the self [18, 20-22, 538] (see Table 25 and Table 26 for more details). There is evidence that increases in positive mood and anxiety increased with dose [18, 20, 82, 604]. Healthy controls reported greater interpersonal closeness to others [23, 82-85, 579]. It is uncertain whether the increases in positive and negative mood occurred simultaneously or at different times throughout the duration of MDMA effects; evidence from two different teams suggests that peaks in negative mood may precede peaks in positive mood [22, 586].

People have reported feeling anxious or experiencing negative derealization while under the influence of MDMA, including increased anxiety related to loss of control and experiences of racing or blocked thoughts [18, 21, 23]. More information on the effects of MDMA on affect may be found in Section 6.4.6 Abuse Potential.

An examination of personality assessed prior to and after receiving MDMA-assisted psychotherapy from a sponsor-supported study (MP-1) reported increased openness to the experience and decreased neuroticism after MDMA when compared with placebo [605], a finding similar to those reported in studies of people given the classic psychedelic psilocybin [606, 607]. Wagner and colleagues also found that changes in openness, but not neuroticism, were associated with reductions in PTSD symptoms [605].

MDMA may alter detection and receptivity to expressions of emotion. Findings suggest that MDMA might change the way emotional facial expressions might be processed or the response to them. MDMA improved accuracy of recognizing expressions of positive mood and were less accurate in recognizing expressions of negative mood [85], and reduced amygdalar response to angry faces to suggest possibly an altered response to expressions of anger [41]. Despite contradictory findings from a naturalistic study, a controlled trial reported that MDMA impaired detection of expressions of fear [608]. An fMRI study found that 0.75 and 1.5 mg/kg MDMA reduced signaling in the amygdala in response to angry faces when compared with placebo without changing the response to faces showing fear [41]. MDMA reduced the aversiveness of hearing sounds associated with negative emotions [609]. In addition, and contrary to the finding in the early naturalistic study described above, there is some evidence that MDMA might produce selective difficulty in recognizing faces expressing fear [56, 541].

At least four research teams published relevant findings in studies of healthy volunteers that examine the effects of MDMA on social cognition with several experimental paradigms assessing brain activity during episodic memory recall and contributions of oxytocin and cortisol to the acute effects of MDMA [41, 598, 602, 610, 611]. Findings include reduced reactivity to simulated social exclusion, reduced negative emotional response to self-selected "worst" memories, increased use of language related to interpersonal closeness, increased emotional empathy, and increased perceived partner empathy (see Appendix Table 1: Summary of Investigator-Initiated Trials with MDMA). Taken together, this research lends greater support that MDMA possesses unique psychological effects, distinct from psychostimulants that can be beneficial when combined with psychotherapy.

MDMA in healthy participants makes social activities more attractive [612], people more generous toward a friend [613], and more willing to trust a stranger in a "trust game." Rather than increasing trust indiscriminately, trust was given only to trustworthy actors [610]. Studies in healthy controls, comparing doses between 0.75 and 1 mg/kg and 1.5 to 2 mg/kg, suggest that the higher dose produced greater prosocial effects than the lower dose, while the lower dose may have increased self-reported loneliness and use of empathy-related language [34, 35, 614, 615].

In a study by Bedi and colleagues, MDMA induced changes in semantic speech content measured with natural language learning software [33]. Proximity of speech to the concepts of friend, support, intimacy, rapport, and empathy was increased over placebo in the MDMA group, which may bear some significance for the use of MDMA in therapy. MDMA did not affect the overall structure of participants' speech, and these findings were confirmed in an additional sample using a different method of analysis. The study by Bedi and colleagues reported a greater use of social words and words describing emotions [616]. A systematic examination of statements (discourse) from participants enrolled in MAPS' study MP-1 conducted by an independent researcher found greater attention to and concern for the therapists and others in participants receiving MDMA versus inactive placebo [617].

Sensorimotor Reflex Responses

MDMA does not acutely affect responses on tasks requiring attention and response to visual stimuli or visually presented words [23, 599], but has been shown to interfere with performance on digit-symbol substitution - a measure of attention, psychomotor speed and visual memory [18]. 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 for driving cars [618], though without effects on performance monitoring [619]. Subsequently, a series of studies have thoroughly examined the effects of MDMA on road-tracking and car-following performance in both stimulated and on-the-road driving in normal traffic as part of the Driving Under the Influence of Drugs, alcohol and medicines (DRUID) research consortium funded by a European Union grant. A single-dose of 25 mg, 50 mg, 75 mg, or 100 mg MDMA did not produce any dose- or concentration-related effects on driving performance and was found to be generally safe for driving at therapeutic doses in the absence of sleep loss or alcohol intoxication [620-624]. In one of these studies, driving tests were conducted between 3 and 5 hours after a

dose of 75 mg MDMA. Subjects returned the following day for a repetition of the driving tests between 27 and 29 hours post-MDMA. Although changes in cognitive function and psychomotor skills occurred during peak drug effects, these were not detectable on the following day. Acute effects such as excessive caution and impaired positional memory support refraining from driving or using heavy machinery [625] during Experimental Sessions.

MDMA causes slight changes in visual or auditory perception, including changes in the brightness or colors, sounds seeming closer or farther away, simple visual distortions [17, 18, 20, 21], and altered time perception [20, 22, 23] Participants also experienced altered time perception and changes in meaning or significance of perceptions after MDMA. There is little indication that MDMA produces any strong alterations to the sense of self or control over the experience [20]. Women reported experiencing all subjective effects of MDMA more intensely compared to men, but especially those related to perceptual changes [21, 184, 580]. The effects of MDMA on perception have not been studied in sponsor-supported studies.

Body Temperature

Grob and colleagues noted that in a Phase 1 safety study MDMA was found to cause a significant increase in body temperature in some healthy volunteers [44]. However, these increases were transient and tolerable in a controlled clinical setting. Studies conducted by other researchers reported that doses between 1.5 and 2 mg/kg MDMA produced a slight elevation in body temperature that was not clinically significant [21, 542, 577, 580] and this elevation was unaffected by ambient temperature [211]. Further, 2 mg/kg produced a slight but statistically significant increases in core body temperature with a mean elevation of 0.6°C, at cool (18°C) and warm (30°C) ambient temperatures [211]. A supplemental dose twice as large as the initial dose of MDMA elevated body temperature, but not beyond what was expected after the cumulative dose [260].

Thermogenic effects of MDMA are distinct from malignant hyperthermia and mediated by noradrenergic signaling, which contributes to peripheral effects of MDMA by affecting cutaneous vasoconstriction of blood flow and stimulation of heat production, and attenuated by norepinephrine blocking drugs. Research participants in clinical trials do not engage in vigorous exercise and either sit or lie down throughout duration of drug effects. It may be the case that heat dissipation impaired by a hot environment, heat generation increased by exertion, interactions of serotonergic drugs, and potential disturbance of central heat regulation mechanisms contribute to the occurrence of hyperpyrexia (body temperatures >41°C) in people ingesting Ecstasy in uncontrolled settings.

When compared with placebo, findings from 74 people that were given MDMA in oral doses ranging from 70-150 mg (1.35-1.8 mg/kg) found that men exhibited a greater elevation in body temperature than women when given the dose of MDMA in mg/kg [21]. Subsequent studies have not confirmed this gender difference [41]. A report in a sample of 17 men and women reported higher oral temperatures in women [570]. Prior to correction for number of tests, a study on the effects of serotonin-related genotypes on MDMA reported higher body temperature in people with a variant of the TPH-2 gene,

but these findings were no longer significant after applying corrections [571]. A review of clinical placebo-controlled laboratory studies conducted without sponsor support found that route of measurement influences variability in body temperature findings, with oral and tympanic, but not axillary, temperatures frequently rising above 38°C into moderate hyperthermia ranges at 125 mg MDMA.

6.2.3.2 Cardiovascular System

MDMA produces sympathomimetic effects that include elevation in blood pressure and heart rate, first recorded by Downing [39] and replicated by other research teams in the U.S. and Europe [17, 19-21, 40-42, 542]. MDMA has also been found to decrease respiratory sinus arrhythmia, the natural variation in heart rate over the course of each respiratory cycle [626]. Cardiovascular effects of MDMA typically first appear 30 to 45 minutes after administration [39], peak between 1- and 2-hours post-drug [22, 40], and wane 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 heart rate in a study summarizing and pooling data from a series of human MDMA studies [21]. These studies did not report any discomfort or increased distress accompanying cardiovascular effects.

Elevation in blood pressure above 140/90 mmHg occurred in approximately 5% of research participants receiving a single dose of at least 100 mg of MDMA in Phase 1 research studies [19, 23]. Peiro and colleagues observed elevation in blood pressure above 150/90 mmHg as well as in all 10 participants given 50 mg followed by 100 mg MDMA 2 hours later [260](see Appendix Table 1: Summary of Investigator-Initiated Trials with MDMA). When compared with 100 mg MDMA and placebo given 4 hours apart, two doses of 100 mg 4 hours apart significantly elevated SBP, while other physiological effects were not significantly elevated beyond values seen after a single dose. None of these individuals needed clinical intervention and blood pressure returned to normal as drug effects waned [19, 23, 260].

The α1- and beta-adrenergic receptor antagonist carvedilol is capable of reducing MDMA-induced elevations in blood pressure, heart rate, and body temperature when administered 1 hour before MDMA without affecting the subjective effects of MDMA, indicating the norepinephrine release is primarily responsible for cardiovascular effects of MDMA [223]. Other concomitant antihypertensive medications either alter some of the effects of MDMA [608] or do not significantly reduce MDMA-induced blood pressure elevation [221].

6.2.3.3 Hepatic System and Other Laboratory Values

An examination of liver function as assessed approximately 1 month after MDMA administration in 166 participants, most of them MDMA-naïve, failed to detect any post-drug changes [542]. The first two sponsor-supported Phase 2 studies (MP-1, MP-2) assessed liver function after completion of two or three blinded Experimental Sessions (see Section 6.4.4 Hepatic System and Other Laboratory Values). Values that differ from established age-appropriate norms were evaluated for clinical significance. Laboratory assessments of liver function were not conducted after Experimental Sessions in

subsequent sponsor-supported studies and no AEs related to liver function have been reported in these studies.

Table 6: List of All Clinically Significant Changes in Laboratory Values in Two Participants from MP-2

Laboratory Value	Abnormal Test Value	Value at Baseline	Normal Value/Range	Dose
Bilirubin	2.8	2.2	<2.5 mg/dL	125 mg
ESR	32	2.4	<10 mm	125 mg

Two participants in the MP-2 study reported two clinically significant abnormalities. One was an elevation in bilirubin in a subject with a family history of elevated bilirubin (probably Gilbert's syndrome), a benign liver condition in which the liver does not properly process bilirubin, with the elevation occurring after open-label treatment with 125 mg to 150 mg initial dose of MDMA Family history of mildly elevated bilirubin is considered an indicator of Gilbert's syndrome. Bilirubin levels can be indicative of decreased liver function, but the liver enzymes were normal at that time, supporting the interpretation that the bilirubin levels were slightly elevated compared to baseline due to hereditary factors. The other abnormal laboratory value, an elevation in erythrocyte sedimentation rate (ESR), a marker of inflammation and not a specific liver function marker, occurred in a subject with a medical history of breast cancer. This value was recorded 3 months after the last administration of MDMA as an AE unrelated to the Investigational Product.

Table 7: Average ALT Values at Baseline and 2-Month Follow-up After Two Experimental Sessions in Participants from MP-1

Timepoint	Placebo	125 mg
Baseline	25.6 (13.4) N=8	22.75 (12.89) N=12 [a]
Primary Endpoint After Two Experimental Sessions	26.4 (13.5) N=8	19.7 (12.7) N=13

[1] Post-drug liver panels or other laboratory tests were not conducted in studies subsequent to studies MP-1 and MP-2.

No clinically significant changes in liver function occurred in MP-1. Values for laboratory tests were within the normal range in MP-1. Phase 1 studies conducted outside of sponsor support involving administration of MDMA to healthy volunteers have not published any results of liver function after MDMA administration. There have been no reported adverse effects on the liver from these studies.

6.2.3.4 Renal System

Cardiovascular Effects as correlating with AVP in blood, was detected in women acutely after 125 mg MDMA administration [583], and this finding was reproduced in another study reporting that 47.5 mg MDMA caused an acute rise in AVP and a small decrease in plasma sodium, at a time of day when it would not be expected to change, in an all-male sample. [231].

Norepinephrine release induced by MDMA leads to indirect activation of the AVP system, likely stimulating secretion of copeptin (CTproAVP), a 39-aminoacid glycopeptide that is a C-terminal part of the precursor to pre-proAVP that directly affects AVP. Heart failure is commonly associated with hyponatremia and is also characterized by increased concentrations of basal AVP and CTproAVP in humans [457]. Intra-cardiac pressures, intra-arterial pressures, angiotensin II, pain, and adrenergic (α2) central nervous stimuli can also influence AVP secretion [445]. Increased CTproAVP concentration was described in several studies as a strong predictor of mortality in patients with chronic heart failure and acute heart failure. [446].

6.2.3.5 Immune System

Various groups have studied immunological effects of MDMA in laboratory settings and studies in men conducted by researchers in Spain have found 100 mg MDMA to have immunosuppressive and anti-inflammatory effects [578, 596, 627-629]. 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 (see Appendix Table 1: Summary of Investigator-Initiated Trials with MDMA). Generally, MDMA appeared to decrease the concentration of Th1 cytokines, including IL-2, and increase the amount of Th2 cytokines, including IL-4, measured in blood. Changes of similar magnitude and duration have been previously noted after ingestion of other psychoactive agents such as alcohol or cocaine [628, 629]. Interestingly, meta-analysis and meta-regression of 20 studies investigating inflammatory markers in PTSD found an association with increased IL-6, IL-1α, TNF-α, and INF-α, consistent with chronic low-grade inflammation [271] Any effects of MDMA on these immune markers remain to be tested.

Immunological changes seen after an initial dose of MDMA were enhanced by a second dose of identical size given 4 or 24 hours after the initial dose [596, 630]. Given these data, it is possible that administering a smaller supplemental dose 1.5 to 2.5 hours after the first dose could slightly enhance the immunological effects set in motion by the initial dose of MDMA.

To date, the clinical significance of these immunological findings have not been established and no reports of an increase in infections related to MDMA administration have been found in PTSD studies.

6.2.3.6 Reproductive System

Human data on effects of MDMA during pregnancy is limited. Several epidemiological survey studies have attempted to study this issue and found mixed results [631-633]. 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 [634]. These results were repeated in a 2016 survey of 96 mothers who reported heavier MDMA use (1.3±1.4

tablets per week) during pregnancy. Infants had motor delays from 4 months to 2 years of age that were not attributable to other drug or lifestyle factors [635]. There is no suspicion of human teratogenicity based on class effects of genotoxic potential, and non-clinical reproductive toxicity studies of relevance for early human pregnancy show some positive findings that do not generate strong suspicion of human teratogenicity/fetotoxicity.

6.2.3.7 Cognition and Performance

Research has assessed acute effects of MDMA on perception and cognition acutely after MDMA, commonly at doses between 75 and 125 mg (or 0.5 to 1.5 mg/kg). In these studies, acute subjective effects peaked 90 to 120 minutes after oral administration and returned to pre-drug levels 3 to 6 hours later [23, 615, 618]. Sub-acute effects assessed in controlled and naturalistic studies occurred 1 to 3 days after drug administration, but were no longer apparent 7 to 14 days later [20, 531, 636]. A study of variations in serotonin-related genes across a pooled sample reported that people with a variant of the 5HT2A gene reported experiencing more "good drug effect," "trust," "high mood," and "dreaminess," and people with a variant in the 5HT1A gene reported a higher "good drug effect," "closeness to others", and lower ratings of a "bad drug effect" [571]. People with a variant of the SERT gene reported greater "fear" and 'depression" after MDMA.

A second dose of MDMA 2 hours after the first did not increase subjective effects beyond that of an initial dose, which was interpreted by Peiro and colleagues as an indication of tolerance to these effects [260]. When two 100 mg doses were given 4 hours apart, most subjective effects were comparable to those after a single dose, despite double the amount of plasma MDMA [557]. It is notable that the second dose in this study was identical to the first dose, in contrast to sponsor-supported studies, wherein the second dose was half the size of the initial dose. See Section 6.2.3 Physiological Effects for further details on subjective effects.

Findings from a pooled set of drug-naïve participants reported gender differences in intensity of subjective effects with women reporting greater intensity of all subjective effects, and especially perceptual effects [21], while a separate analysis of pooled samples failed to support these gender effects [538]. A post-hoc analyses of pooled data conducted by the sponsor found that the differences in pharmacokinetic parameters and most likely subjective effects were attributable to differences in body weight rather than gender (data not published).

The effects of MDMA on perception have not been studied within sponsor-supported studies. The perceptual effects of MDMA appear to be the result of direct or indirect action on 5HT2A receptors; co-administration of the 5HT2A antagonist ketanserin reduced reported perceptual alterations, as well as eliminated slight elevations in body temperature after 1.5 mg/kg MDMA [580], while co-administration with the 5HT1A antagonist pindolol did not affect perceptual alteration [184].

6.3 Efficacy of MDMA Across Populations

6.3.1 PTSD

When combined with psychotherapy, MDMA permits people to confront and consider emotionally intense memories, thoughts, or feelings, and perhaps through changes in mood and perception, increase empathy and compassion for others and oneself [3, 54, 81]. In a sub-study of MP-8, the Self Compassion Scale [637] was administered before and 2 months after MDMA-assisted psychotherapy. Preliminary results in this small sub-study (N=7) were promising; participants were low in self-compassion with a mean total score of 2.4±0.63 prior to the study and experienced an increase to moderate self-compassion with a mean total score of 2.8±0.84. In this assessment, self-kindness and a sense of common humanity increased, while self-judgment and feelings of isolation decreased on average within-subjects.

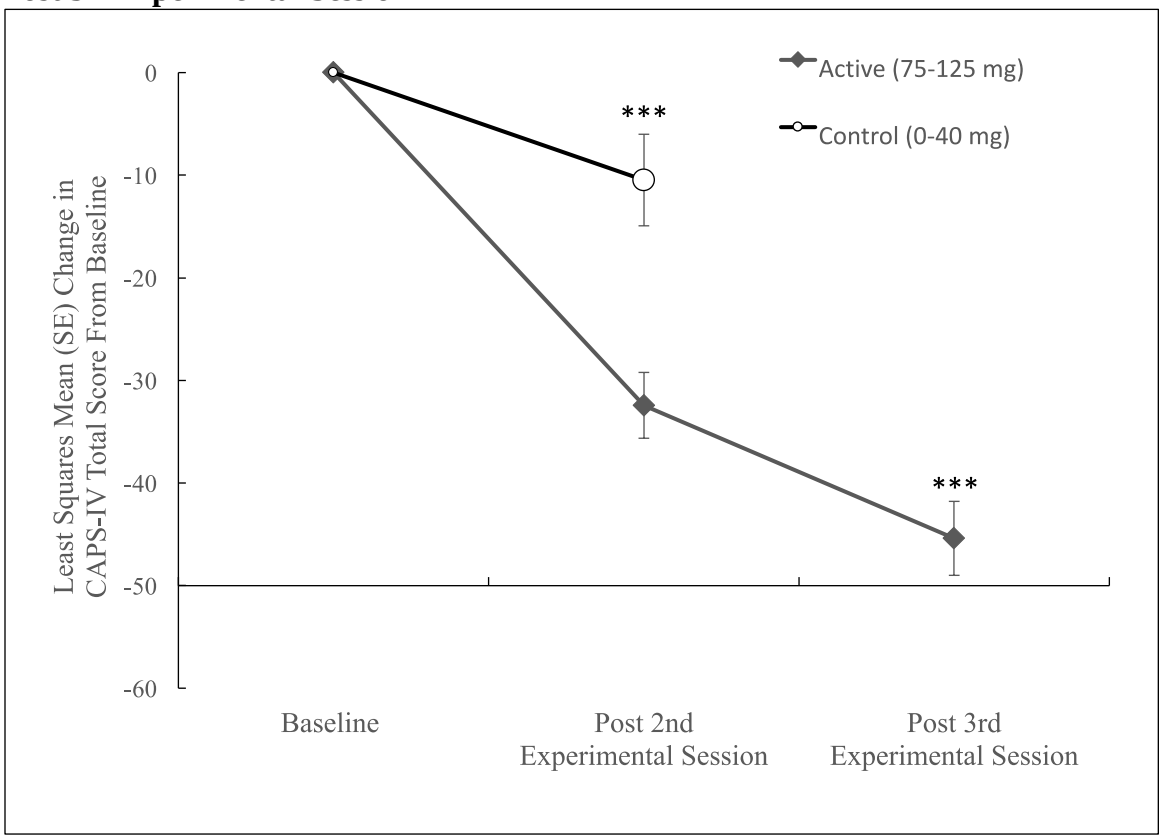
Completed sponsor-supported Phase 2 studies of MDMA-assisted therapies employed recognized clinician-administered gold-standard measures of the condition or symptoms. The primary outcome measure of efficacy in the first six Phase 2 studies of MDMA-assisted psychotherapy was the Clinician Administered PTSD Scale (CAPS-IV) following DSM-IV, an established semi-structured interview conducted by a trained clinician [638-640]. The Total Severity CAPS-IV score encompasses frequency and intensity scores for three symptom domains: re-experiencing, avoidance and hyperarousal. An Independent Rater that does not see the participants during any of the psychotherapy sessions administers the CAPS-IV at the Baseline Visit and at the Primary Endpoint (1 or 2 months after blinded MDMA-assisted psychotherapy sessions). Secondary endpoints include an assessment 1 to 2 months after a third Experimental Session and 12 months after the last treatment.

Analyses of the CAPS-IV Total Severity scores at the Primary Endpoint after two Experimental Sessions in MP-1 found participants receiving MDMA-assisted psychotherapy experienced a clinically and statistically significant decline in PTSD symptoms compared to placebo-assisted psychotherapy [3]. Placebo subject scores dropped 20.5 points 2 months after the second Experimental Session while MDMA subject CAPS scores dropped 58.6 points. The second study (MP-2) found results similar to the MP-1 study, where improvement after three blinded Experimental Sessions with 125 mg MDMA was greater compared to the 25 mg MDMA comparator dose, but the difference between groups was not statistically significant [5]. CAPS-IV scores declined 15.7 points over time for the eight participants given 125 mg MDMA; on the other hand, CAPS-IV scores increased slightly by 4.3 points over time for the four participants given the comparator dose.

Figure 3 below show pooled mean Total Severity CAPS-IV scores for sponsor-supported studies (MP-1, MP-2, MP-4, MP-8, MP-9, MP-12), as reported in a comparison of active dose (75 to 125 mg) versus placebo dose (placebo to 40 mg) MDMA at Primary Endpoint, 1 to 2 months after a second Experimental Session and 1 to 2 months after the third Experimental Session (End of Stage 1) [1]. Despite slight differences in study designs, including length of time post second Experimental Session to outcome assessment (3 to 8 weeks), and language of the CAPS (English or translated), these

results demonstrate reproducibility and generalizability across multiple international studies of MDMA-assisted psychotherapy in the treatment of chronic PTSD. Placebo and comparator groups cross over to Stage 2 after the Primary Endpoint; therefore, CAPS was not administered at the End of Stage 1 for these groups. Active dose groups (100 mg and 125 mg) do not crossover, hence no data for Stage 2 endpoints.

Figure 3: Least Squares Mean Estimates of Change in CAPS-IV from Baseline to Post 3rd Experimental Session

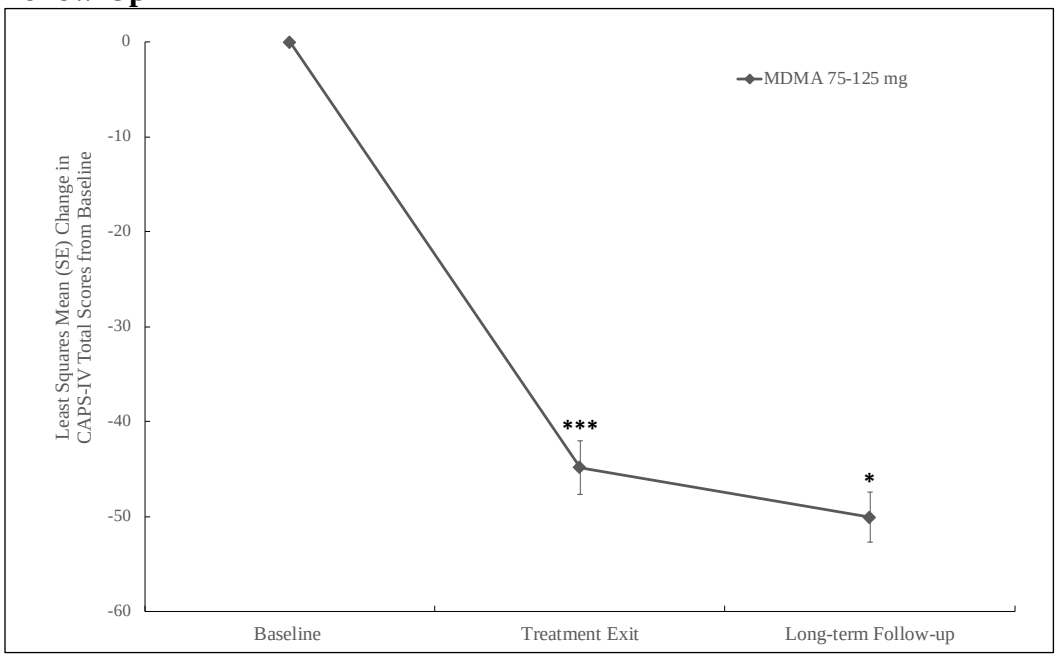


Across studies, CAPS-IV scores are downward trending at the Primary Endpoint, after two Experimental Sessions of MDMA-assisted psychotherapy. Primary endpoint results after active doses of 75 to 125 mg initial dose, with an optional supplemental half-dose administered 1.5 to 2.5 hours later, appear lower than placebo or comparator dose results after two Experimental Sessions. Two-month follow-up results at the End of Stage 1 after a blinded or open-label third Experimental Session demonstrate further mean decreases in CAPS score.

Across studies, CAPS-IV scores trended downward at the Secondary Endpoint after two open-label Experimental Sessions of MDMA-assisted psychotherapy, consistent with Stage 1 results. Secondary endpoint results in the crossover set receiving an active dose of 100 to 125 mg MDMA after receiving comparator dose or placebo in Stage 1 are in range with participants receiving active doses in Stage 1. At treatment exit (the end of Stage 1 or 2, final assessment), CAPS-IV severity scores dropped 44.8 points (SD 2.82), Cohen's d effect size of 1.58 [47]. Symptom severity remained essentially the same as treatment exit when assessed at least 12 months later, with scores dropping 5.2 more points, indicating an enduring reduction in symptoms after MDMA-assisted

psychotherapy (Figure 4). The number of participants who no longer met PTSD criteria increased from treatment exit (56.0%) to long-term follow-up (67.0%) [47]. However, the lack of a control group at 12-month follow-up limited the interpretation of these results and warrants further investigation.

Figure 4: Least Squares Mean Change in CAPS-IV from Baseline to Long-Term Follow-Up



Subsequent to completing these studies, the sponsor assessed PTSD symptoms with the CAPS-5, designed to capture the diagnostic criteria for PTSD found in the DSM-5. Like the CAPS-IV, the new version of the CAPS is a structured interview, and it was administered by an Independent Rater who had not been present during any psychotherapy sessions. CAPS-5 total severity scores range from 0 to 80. CAPS-5 was employed in study MPVA-1, MP16 and MP17. It is also in use for the ongoing study MAPP1, and for planned studies of MDMA-assisted psychotherapy in people with PTSD.

6.3.2 Social Anxiety in Autistic Adults

The primary outcome measure for the study of social anxiety in people on the autism spectrum is the Liebowitz Social Anxiety Scale (LSAS). This observer-blind measure is an established clinician-administered measure of social anxiety, assessing fear and avoidance in different situations. The LSAS consists of 24 items, with each item rated on a four-point scale (from 0 to 3), with subscales for performance fear, performance avoidance, social fear, and social avoidance.

Data was analyzed and findings appear in the following publication [536]. Improvement in LSAS scores from the Baseline Visit to the Primary Endpoint was significantly greater for MDMA group compared to the placebo group (P=0.037), and placebo-subtracted Cohen's d effect size was very large (d=1.4, CI: -0.074, 2.874). Change in LSAS scores

from the Baseline Visit to 6-month follow-up showed similar positive results (P=0.036), with a Cohen's d effect size of 1.1 (CI: -0.307, 2.527). The study safety and efficacy data were published [536].

6.3.3 Anxiety Associated with Life-Threatening Illness

MAPS is studying the effects of MDMA-assisted psychotherapy on people experiencing anxiety as they face a potentially life-threatening illness. A manuscript containing results has been submitted for publication and currently under peer review. Once published results will be presented in the IB.

6.4 Safety of MDMA in Humans

All sponsor-supported safety data (adverse events, spontaneously reported reactions, vitals during Experimental Sessions, and suicidal ideation and behavior) are presented in this IB through a cutoff date of 30 April 2020 unless indicated otherwise. For more information on completed, ongoing and planned sponsored studies, please see Table 4 and Table 5.

Safety was addressed and closely monitored through several measures in these studies. Vital signs, concomitant medications, unexpected, and expected AEs were collected in all studies. Suicidal ideation and behavior were formally measured with the Columbia Suicide Severity Rating Scale (C-SSRS) in all but the MP-1 and MP-2 studies. Three completed studies (MP-1, MP-12, MP-4) measured cognitive function before and after treatment. Psychological distress during psychotherapy sessions was assessed in most Phase 2 studies with the single-item Subjective Units of Distress (SUD) scale.

Partial safety data from the Phase 1 study MT-1 in healthy volunteers are not presented in the current report since the data remain blinded. There have been no Serious Adverse Events (SAEs), or clinically significant changes in vital signs in the MT-1 study. No medical intervention has been required for AEs during this study to date.

The most common reactions across all studies in which these reactions were collected were transient and decreased over time, as the drug was metabolized during treatment sessions and excreted over the next 24 hours with the majority of reactions resolving within several days and up to 1 week after dosing. Overall, across treatment groups, the most frequently reported spontaneous reactions or adverse events were anxiety, headache, and fatigue. In the active MDMA dose groups, participants reported spontaneously reported reactions including dry mouth, diarrhea, heavy legs, impaired judgment, and nystagmus; none were reported as severe and all had resolved by day 7 following the Experimental Session. The most frequently reported severe reactions were anxiety, nausea, insomnia, and tight jaw (see Table 8-13 and Appendix Tables 17-21). In the active MDMA dose groups, ≥10% of participants reported the following reactions had not resolved 7 days following the Experimental Session: anxiety, fatigue, difficulty concentrating, increased irritability, insomnia, and low mood.

The half-life of MDMA doses used in these studies was 8 to 9 hours and the majority of AEs have been transient, resolving within 2 to 3 days after MDMA had been metabolized

and excreted. Measures of adverse events indicated that >5% of active MDMA dose group participants reported muscle tightness and nausea. Severe anxiety, insomnia, fatigue, nausea, muscle tightness, and depressed mood were commonly reported in PTSD studies supported by the sponsor. These reactions also overlapped with symptoms of pre-existing conditions in medical history associated with PTSD (depression, somatic symptoms, insomnia, anxiety), which might have influenced the frequency of events observed during clinical trials of MDMA-assisted psychotherapy.

In MAPS-sponsored PTSD studies MP-1 to MP-12, body temperature above (1°C above pre-drug reading) was detected in 44% (42 of 95) participants who received any dose of MDMA during blinded sessions and 50% (39 of 78) participants receiving 100 to 150 mg MDMA during open-label sessions. Note that body temperature above 1°C above pre-drug reading was observed in 20% (2 of 10) of participants who received placebo. End of session temperature readings were lower than peak drug readings, though they remained above pre-drug measurements. Body temperature increases that were 1°C or more above initial temperature occurred in all dose groups, suggesting a minimal role for dose. The maximum body temperature observed for any subject receiving MDMA was 38.7°C, observed after a 100 mg MDMA blinded session, and during open-label sessions. No participants required medical intervention to decrease body temperature and values returned to baseline as drug effects waned. There was no need for medical intervention in addressing elevated body temperature. Body temperature measured during Experimental Sessions in sponsor-supported studies of PTSD was commensurate with values seen in Phase 1 clinical trials described above.

In MP16 and MP17, vital signs were assessed on the day of MDMA-assisted sessions prior to drug dosing, just before the optional supplemental dose (midpoint), and at the end of the session. The maximum body temperature observed for any subject receiving MDMA across MP16 and MP17 was 38.7°C and the mean (SD) temperature prior to the supplemental dose was 37.1°C.

In the MAPS study MAA-1, body temperature 1°C above pre-drug reading was detected in 28.6% (2 of 7) participants who received 100 mg of MDMA during a blinded session. Body temperature above the 1°C increase predetermined as cause for increased assessment did not occur during open-label sessions with 75 or 125 mg MDMA. The maximum body temperature observed for any subject receiving MDMA in MAA-1 was 37.7°C. No participants required medical intervention to decrease body temperature and values dropped below peak values or returned to baseline as drug effects waned. Body temperature measurements in this sample were similar to those reported in Phase 1 studies and the sample of people with PTSD (See Appendix Table 2 for data).

In the MAPS study-Phase 2 clinical trial of MDMA-assisted psychotherapy for anxiety in relation to a life-threatening illness (MDA-1), body temperature rose 1°C above pre-drug reading in 53.8% (7 of 13) of participants receiving MDMA during blinded Experimental Sessions and in none of the participants given placebo during blinded sessions. Body temperature rose 1°C above pre-drug reading in 52.9% (9 of 17) participants during open-label sessions. Body temperature recorded at end of session was lower than peak body temperature. The maximum body temperature observed for any subject receiving 125 mg

MDMA was 39.9°C. No participants required medical intervention to decrease body temperature and values returned to baseline as drug effects waned.

In MPVA-1, vital signs were assessed on the day of MDMA-assisted sessions prior to drug dosing, just before the optional supplemental dose (midpoint), and at the end of the session. The maximum body temperature observed for any subject receiving 75 or 100 mg MDMA was 38.4°C and the mean (SD) temperature prior to the supplemental dose was 37.1°C (SD=0.53) in the CSO participant and 37.2°C (SD=0.48) in the PTSD+ participant.

Based on the literature, MDMA is expected to produce elevations in body temperature with possible influence of ambient temperature. In the above MAPS-sponsored studies, adjustments were made to the ambient temperature and to air circulation in the room in response to observed elevation in body temperatures, but no participants required medical intervention to decrease body temperature, and values returned to baseline as drug effects waned. In conclusion, controlled settings for treatments with MDMA-assisted psychotherapy were optimized with the capacity to control the ambient temperature for subject comfort, though there is no evidence that these measures significantly influenced or were needed for control of core body temperature.

6.4.1 Adverse Events

6.4.1.1 Commonly Reported Reactions

Common AEs of MDMA reported in non-sponsor supported Phase 1 studies in healthy volunteers include elevation in blood pressure and heart rate, increased anxiety or dysphoria, and dilated pupils [18-21]. Some reports indicated decreased rather than increased alertness [18]. Other common AEs reported in controlled studies of MDMA include reduced appetite, dizziness, tight jaw, bruxism (tooth-grinding), disturbance in attention, impaired gait or balance, dry mouth, and thirst. Participants in some studies also reported or exhibited changes in cognition, such as increases in speed of thought or thought blocking, facilitated imagination or recall [23], and unusual thoughts or ideas [20]. Other less commonly reported events include paraesthesia (unusual body sensations) such as tingling, or feeling hot or cold. MDMA can produce anxiety in healthy volunteers [20, 21, 23]. These effects are transient and recede as drug effects wane. One study found that women were more likely to report these events than men [21], while another study failed to support gender differences in reporting AEs [538]

The most commonly reported AEs from Phase 1 studies published between 1986 and 2012 were used to develop a list of common reactions, or Spontaneously Reported Reactions, to record daily occurrence, duration and severity [20, 23, 39, 54, 81, 221, 224, 576, 580, 582, 586, 599]. Based on the reports, 24 reactions were identified to be tracked during sponsor-supported studies MP-1 and MP-2, and three were added after examining data from the first sponsor-supported study in a PTSD sample (MP-1). The investigators noted that participants in MP-1 reported greater incidence of diarrhea and muscle tightness, which were added to the list, and further observation led to the addition of impaired judgment. Based on the half-life of active MDMA doses being 7 to 9 hours, it was most important to collect reactions on the day of drug administration and the

following 7 days after each Experimental Session. The subset of AEs referred to as spontaneously reported reactions included: anxiety, depressed mood, insomnia, obsessive rumination, restlessness, irritability, headache, disturbance in attention, dizziness, parasthesia, judgment impaired, hypersomnia, nausea, diarrhea, fatigue, asthenia, feeling cold, muscle tension, decreased appetite, hyperhidrosis, disturbed gait, dry mouth, thirst, sensation of heaviness, somnolence, and nystagmus.

In sponsor-supported Phase 2 studies, researchers recorded any spontaneous (unsolicited) reports of common reactions on the day of each Experimental Session and 7 days after. The same severity coding system for AEs was employed throughout all studies, based on limitation in daily function. Table 8 and Table 9 below display data from studies investigating MDMA-assisted psychotherapy for PTSD (MP-1, MP-2, MP-4, MP-8, MP-9 and MP-12), social anxiety in autistic adults (MAA-1) (see Appendix Table 17), and anxiety associated with life-threatening illness (MDA-1) (see Appendix Table 18 and Appendix Table 19).

6.4.1.2 Spontaneously Reported Reactions

The most commonly reported AEs from Phase 1 studies published between 1986 and 2012 were used to develop a list of common adverse reactions to MDMA, or Spontaneously Reported Reactions, to record daily occurrence, duration and severity [20, 23, 39, 54, 81, 221, 224, 576, 580, 582, 586, 599]. Based on the reports, 24 reactions were identified to be tracked during sponsor-supported studies MP-1 and MP-2, and three were added after examining data from the first sponsor-supported study in a PTSD sample (MP-1). The investigators noted that participants in MP-1 reported greater incidence of diarrhea and muscle tightness, which were added to the list, and further observation led to the addition of impaired judgment. Based on the half-life of active MDMA doses being 7 to 9 hours, it was most important to collect reactions on the day of drug administration and the following 7 days after each Experimental Session. The subset of AEs referred to as spontaneously reported reactions included: anxiety, depressed mood, insomnia, obsessive rumination, restlessness, irritability, headache, disturbance in attention, dizziness, parasthesia, judgment impaired, hypersomnia, nausea, diarrhea, fatigue, asthenia, feeling cold, muscle tension, decreased appetite, hyperhidrosis, disturbed gait, dry mouth, thirst, sensation of heaviness, somnolence, and nystagmus.

In sponsor-supported Phase 2 studies, researchers recorded any spontaneous (unsolicited) reports of common reactions on the day of each Experimental Session and 7 days after. The same severity coding system for AEs was employed throughout all studies, based on limitation in daily function. Table 8 and Table 9 below display data from studies investigating MDMA-assisted psychotherapy for PTSD (MP-1, MP-2, MP-4, MP-8, MP-9 and MP-12), social anxiety in autistic adults (MAA-1) (see Appendix Tables 17), and anxiety associated with life-threatening illness (MDA-1) (see Appendix Tables18 and Appendix Table 19).

Spontaneous Reactions in PTSD Studies

In Table 8, the relative incidence of spontaneously reported reactions (SRR), which occurred during Experimental Sessions, are summarized for studies MP-1, MP-2, MP-4,

MP-8, MP-9, and MP-12 (N=105). SRR's were collected with AEs in MP16, MP17, and Phase 3 trials. In the placebo group (N=10), participants most frequently reported anxiety (n=9), insomnia (n=9), headache (n=8), and fatigue; severe SRRs included anxiety. (n=7). In subjects who received blinded 25 to 40 mg MDMA (N=21), most frequently reported SRRs included headache (n=14), fatigue (n=11), anxiety (n=8), and muscle tension (n=7); severe SRRs included anxiety (n=1), insomnia (n=1), lack of appetite (n=1), and needing more sleep (n=1). In subjects who received blinded 75 to 125 mg MDMA (N=74), frequently reported SRRs included anxiety (n=52), tight jaw (n=46), headache (n=38), fatigue (n=36), and lack of appetite (n=35); severe SRRs included anxiety (n=5), nausea (n=4), tight jaw (n=4), dizziness (n=2), fatigue (n=2), increased irritability (n=1), insomnia (n=1), lack of appetite (n=1), low mood (n=1), and restlessness (n=1). Similarly, in participants who received open-label 100 mg-150 mg MDMA (N=78), the most frequently reported SRRs were tight jaw (n=47), anxiety (n=38), lack of appetite (n=38), headache (n=35), and fatigue (n=33); and severe SRRs included anxiety (n=8), insomnia (n=5), tight jaw (n=3), headache (n=2), nausea (n=2), increased irritability (n=1), lack of appetite (n=1), and sensitivity to cold (n=1).

Overall, across placebo and active dose treatment groups, the most frequently reported SRRs were anxiety, headache, and fatigue. There were several SRRs that were not reported in the placebo group but were reported in either the active blinded 75 to 125 mg MDMA or open-label 100 to 150 mg MDMA groups: dry mouth, diarrhea, heavy legs, impaired judgement, and nystagmus; none of which were reported as severe. All of these SRRs were resolved by 7-day follow-up after the Experimental Sessions (Table 9). For other SRRs, in the active MDMA dose groups, those that were not resolved by 7-day follow-up after Experimental Sessions in ≥10% of participants included anxiety (25.7% blinded, 17.9% open-label), fatigue (12.2% blinded, 10.3% open-label), difficulty concentrating (9.5% blinded only), increased irritability (10.8% blinded only), insomnia (10.8% blinded only), and low mood (17.6% blinded only). The placebo group had significantly fewer participants which limits direct comparison against the active MDMA dose groups. Nonetheless, in a total of 10 participants, a large proportion of the placebo sample also reported anxiety, fatigue, and insomnia at 7-day follow-up. The remaining SRRs that were unresolved at 7-day follow-up that could have been linked to active MDMA were difficulty concentrating, increased irritability, and low mood. Studies with larger and more balanced sample sizes are needed to make direct comparisons against placebo vs. active dose MDMA groups to elucidate whether SRRs had occurred during and/ or after Experimental Sessions. In the meantime, clinical actions are taken to closely monitor all unresolved SRRs throughout the treatment period and later assessed at long-term follow-up.

Table 8: Relative Incidence of Spontaneously Reported Reactions at Any Severity During Experimental Sessions in Sponsor-Supported Phase 2 PTSD Studies of MDMA-Assisted Psychotherapy MP-1, MP-2, MP-4, MP-9, MP-8, MP-12 (N=105)

Dose	Blinded Placebo (N=10) N (%)	Blinded 25-40 mg (N=21) N (%)	Blinded 75-125 mg (N=74) N (%)	Open-label 100-150 mg (N=78)[A] N (%)
Anxiety	9 (90.0)	8 (38.1)	52 (70.3)	38 (48.7)
Severe	4 (40.0)	1 (4.8)	5 (6.8)	8 (10.3)
Diarrhea[a]	---	---	---	3 (3.8)
Severe	---	---	---	---
Difficulty Concentrating	1 (10.0)	3 (14.3)	16 (21.6)	14 (17.9)
Severe	---	---	---	---
Dizziness	2 (20.0)	4 (19.0)	29 (39.2)	23 (29.5)
Severe	---	---	2 (2.7)	---
Drowsiness	2 (20.0)	2 (9.5)	10 (13.5)	8 (10.3)
Severe	---	---		---
Dry Mouth	---	5 (23.8)	15 (20.3)	20 (25.6)
Severe	---	---	---	---
Fatigue	7 (70.0)	11 (52.4)	36 (48.6)	33 (42.3)
Severe	---	---	2 (2.7)	---
Headache	8 (80.0)	14 (66.7)	38 (51.4)	35 (44.9)
Severe	---	---	---	2 (2.6)
Heavy Legs	---	---	9 (12.2)	5 (6.4)
Severe	---	---	---	---
Impaired Gait/Balance	1 (10.0)	3 (14.3)	18 (24.3)	17 (21.8)
Severe	---	---	---	---
Impaired Judgment[a]	---	---	---	1 (1.3)
Severe	---	---	---	---
Increased Irritability	3 (30.0)	1 (4.8)	7 (9.5)	5 (6.4)
Severe	---	---	1 (1.4)	1 (1.3)
Insomnia	9 (90.0)	3 (14.3)	21 (28.4)	22 (28.2)
Severe	---	1 (4.8)	1 (1.4)	5 (6.4)
Tight Jaw	3 (30.0)	3 (14.3)	46 (62.2)	47 (60.3)
Severe	---	---	4 (5.4)	3 (3.8)
Lack of Appetite	2 (20.0)	5 (23.8)	35 (47.3)	38 (48.7)
Severe	---	1 (4.8)	1 (1.4)	1 (1.3)
Low Mood	2 (20.0)	2 (9.5)	18 (24.3)	7 (9.0)
Severe	---	---	1 (1.4)	---
Muscle Tension[a]	2 (20.0)	7 (33.3)	27 (36.5)	29 (37.2)
Severe	---	---	---	---
Nausea	3 (30.0)	4 (19.0)	29 (39.2)	29 (37.2)
Severe	---	---	4 (5.4)	2 (2.6)
Need More Sleep	3 (30.0)	4 (19.0)	7 (9.5)	2 (2.6)
Severe	---	1 (4.8)	---	---
Nystagmus	---	---	10 (13.5)	10 (12.8)
Severe	---	---	---	---
Paresthesia	---	1 (4.8)	9 (12.2)	7 (9.0)
Severe	---	---	---	---
Perspiration	1 (10.0)	2 (9.5)	24 (32.4)	26 (33.3)
Severe	---	---	---	---
Restlessness	2 (20.0)	5 (23.8)	26 (35.1)	26 (33.3)
Severe	---	---	1 (1.4)	---
Ruminations	1 (10.0)	3 (14.3)	11 (14.9)	5 (6.4)

Severe	---	---	---	---
Sensitivity to Cold	2 (20.0)	5 (23.8)	28 (37.8)	22 (28.2)
Severe	---	---	---	1 (1.3)
Thirst	1 (10.0)	2 (9.5)	18 (24.3)	16 (20.5)
Severe	---	---	---	---
Weakness	1 (10.0)	---	7 (9.5)	7 (9.0)
Severe	---	---	---	---

[a] Spontaneously reported reactions were not collected during studies MP16 and MP17

Table 9: Relative Incidence of Spontaneously Reported Reactions During Telephone Contact on Day 1-7 After Experimental Sessions in Sponsor-Supported Phase 2 PTSD Studies of MDMA-Assisted Psychotherapy MP-1, MP-2, MP-4, MP-8, MP-9, MP-12

Post-drug	Day 1 N (%)	Day 2 N (%)	Day 3 N (%)	Day 4 N (%)	Day 5 N (%)	Day 6 N (%)	Day 7 N (%)
Anxiety							
Blinded Placebo (N=10)	7 (70.0)	6 (60.0)	5 (50.0)	6 (60.0)	6 (60.0)	6 (60.0)	5 (50.0)
25-40 mg Blinded (N=21)	2 (9.5)	7 (33.3)	7 (33.3)	7 (33.3)	7 (33.3)	5 (23.8)	2 (9.5)
75-125 mg Blinded (N=74)	23 (31.1)	33 (44.6)	36 (48.6)	25 (33.8)	28 (37.8)	32 (43.2)	19 (25.7)
Open-label 100-150 mg (N=78)	19 (24.4)	25 (32.1)	31 (39.7)	28 (35.9)	31 (39.7)	22 (28.2)	14 (17.9)
Diarrhea [a]							
Blinded Placebo (N=2)	---	---	---	---	---	---	---
25-40 mg Blinded (N=16)	---	---	---	1 (6.3)	1 (6.3)	1 (6.3)	1 (6.3)
75-125 mg Blinded (N=50)	1 (2.0)	1 (2.0)	1 (2.0)	1 (2.0)	---	1 (2.0)	---
Open-label 100-150 mg (N=62)	---	---	---	---	---	---	---
Difficulty Concentrating							
Blinded Placebo (N=10)	3 (30.0)	3 (30.0)	3 (30.0)	3 (30.0)	3 (30.0)	4 (40.0)	1 (10.0)
25-40 mg Blinded (N=21)	2 (9.5)	3 (14.3)	2 (9.5)	---	1 (4.8)	---	---
75-125 mg Blinded (N=74)	8 (10.8)	7 (9.5)	11 (14.9)	8 (10.8)	10 (13.5)	9 (12.2)	7 (9.5)
Open-label 100-150 mg (N=78)	6 (7.7)	6 (7.7)	4 (5.1)	4 (5.1)	3 (3.8)	3 (3.8)	---
Dizziness							
Blinded Placebo (N=10)	1 (10.0)	1 (10.0)	1 (10.0)	---	1 (10.0)	---	---
25-40 mg Blinded (N=21)	2 (9.5)	1 (4.8)	1 (4.8)	1 (4.8)	---	---	---
75-125 mg Blinded (N=74)	6 (8.1)	8 (10.8)	7 (9.5)	6 (8.1)	5 (6.8)	6 (8.1)	3 (4.1)
Open-label 100-150 mg (N=78)	4 (5.1)	---	2 (2.6)	2 (2.6)	2 (2.6)	2 (2.6)	1 (1.3)
Drowsiness							
Blinded Placebo (N=10)	1 (10.0)	1 (10.0)	1 (10.0)	---	1 (10.0)	---	---
25-40 mg Blinded (N=21)	2 (9.5)	1 (4.8)	---	---	---	---	---
75-125 mg Blinded (N=74)	1 (1.4)	---	2 (2.7)	1 (1.4)	---	1 (1.4)	1 (1.4)
Open-label 100-150 mg (N=78)	4 (5.1)	4 (5.1)	2 (2.6)	1 (1.3)	---	---	---
Dry Mouth							
Blinded Placebo (N=10)	---	---	---	---	---	---	---
25-40 mg Blinded (N=21)	---	1 (4.8)	---	---	---	---	---
75-125 mg Blinded (N=74)	7 (9.5)	1 (1.4)	4 (5.4)	1 (1.4)	---	1 (1.4)	---
Open-label 100-150 mg (N=78)	4 (5.1)	3 (3.8)	---	---	---	1 (1.3)	---
Fatigue							

Blinded Placebo (N=10)	6 (60.0)	4 (40.0)	4 (40.0)	6 (60.0)	7 (70.0)	5 (50.0)	4 (40.0)
25-40 mg Blinded (N=21)	12 (57.1)	8 (38.1)	6 (28.6)	5 (23.8)	5 (23.8)	5 (23.8)	5 (23.8)
75-125 mg Blinded (N=74)	46 (62.2)	34 (45.9)	29 (39.2)	24 (32.4)	23 (31.1)	23 (31.1)	9 (12.2)
Open-label 100-150 mg(N=78)	36 (46.2)	38 (48.7)	34 (43.6)	22 (28.2)	20 (25.6)	13 (16.7)	8 (10.3)
Headache							
Blinded Placebo (N=10)	5 (50.0)	2 (20.0)	1 (10.0)	1 (10.0)	---	---	---
25-40 mg Blinded (N=21)	8 (38.1)	3 (14.3)	2 (9.5)	2 (9.5)	2 (9.5)	2 (9.5)	2 (9.5)
75-125 mg Blinded (N=74)	19 (25.7)	10 (13.5)	7 (9.5)	9 (12.2)	7 (9.5)	8 (10.8)	3 (4.1)
Open-label 100-150 mg (N=78)	23 (29.5)	9 (11.5)	3 (3.8)	4 (5.1)	5 (6.4)	5 (6.4)	---
Heavy Legs							
Blinded Placebo (N=10)	---	---	---	---	---	---	---
25-40 mg Blinded (N=21)	---	---	---	---	---	1 (4.8)	---
75-125 mg Blinded (N=74)	3 (4.1)	1 (1.4)	---	---	---	1 (1.4)	---
Open-label 100-150 mg (N=78)	---	1 (1.3)	2 (2.6)	---	---	---	---
Impaired Gait/Balance							
Blinded Placebo (N=10)	---	---	1 (10.0)	---	---	---	---
25-40 mg Blinded (N=21)	---	---	---	---	---	---	---
75-125 mg Blinded (N=74)	4 (5.4)	---	1 (1.4)	1 (1.4)	1 (1.4)	2 (2.7)	---
Open-label 100-150 mg (N=78)	2 (2.6)	---	---	---	---	---	---
Impaired Judgment [a]							
Blinded Placebo (N=2)	---	---	---	---	---	---	---
25-40 mg Blinded (N=16)	1 (6.3)	1 (6.3)	1 (6.3)	---	---	---	---
75-125 mg Blinded (N=50)	---	---	---	---	---	---	---
Open-label 100-150 mg (N=62)	---	---	---	---	---	---	---
Increased Irritability							
Blinded Placebo (N=10)	2 (20.0)	2 (20.0)	3 (30.0)	2 (20.0)	3 (30.0)	3 (30.0)	---
25-40 mg Blinded (N=21)	3 (14.3)	3 (14.3)	3 (14.3)	2 (9.5)	2 (9.5)	1 (4.8)	---
75-125 mg Blinded (N=74)	12 (16.2)	13 (17.6)	14 (18.9)	11 (14.9)	11 (14.9)	15 (20.3)	8 (10.8)
Open-label 100-150 mg (N=78)	3 (3.8)	4 (5.1)	5 (6.4)	12 (15.4)	6 (7.7)	7 (9.0)	1 (1.3)
Insomnia							
Blinded Placebo (N=10)	5 (50.0)	3 (30.0)	5 (50.0)	4 (40.0)	5 (50.0)	7 (70.0)	4 (40.0)
25-40 mg Blinded (N=21)	8 (38.1)	8 (38.1)	6 (28.6)	5 (23.8)	4 (19.0)	7 (33.3)	2 (9.5)
75-125 mg Blinded (N=74)	37 (50.0)	20 (27.0)	21 (28.4)	16 (21.6)	19 (25.7)	13 (17.6)	8 (10.8)
Open-label 100-150 (N=78)	19 (24.4)	16 (20.5)	17 (21.8)	15 (19.2)	11 (14.1)	10 (12.8)	6 (7.7)
Tight Jaw							
Blinded Placebo (N=10)	2 (20.0)	---	---	---	---	---	---
25-40 mg Blinded (N=21)	---	2 (9.5)	1 (4.8)	2 (9.5)	2 (9.5)	1 (4.8)	1 (4.8)

75-125 mg Blinded (N=74)	19 (25.7)	11 (14.9)	2 (2.7)	6 (8.1)	5 (6.8)	3 (4.1)	5 (6.8)
Open-label 100-150 mg (N=78)	14 (17.9)	6 (7.7)	3 (3.8)	5 (6.4)	3 (3.8)	2 (2.6)	3 (3.8)
Lack of Appetite							
Blinded Placebo (N=10)	---	---	---	---	---	---	---
25-40 mg Blinded (N=21)	5 (23.8)	3 (14.3)	3 (14.3)	1 (4.8)	1 (4.8)	1 (4.8)	---
75-125 mg Blinded (N=74)	21 (28.4)	17 (23.0)	11 (14.9)	10 (13.5)	7 (9.5)	9 (12.2)	6 (8.1)
Open-label 100-150 mg (N=78)	20 (25.6)	10 (12.8)	8 (10.3)	5 (6.4)	6 (7.7)	3 (3.8)	2 (2.6)
Low Mood							
Blinded Placebo (N=10)	2 (20.0)	1 (10.0)	1 (10.0)	4 (40.0)	3 (30.0)	3 (30.0)	1 (10.0)
25-40 mg Blinded (N=21)	4 (19.0)	5 (23.8)	5 (23.8)	4 (19.0)	5 (23.8)	4 (19.0)	4 (19.0)
75-125 mg Blinded (N=74)	20 (27.0)	25 (33.8)	22 (29.7)	24 (32.4)	20 (27.0)	14 (18.9)	13 (17.6)
Open-label 100-150 mg (N=78)	13 (16.7)	17 (21.8)	12 (15.4)	12 (15.4)	13 (16.7)	4 (5.1)	3 (3.8)
Muscle Tension [a]							
Blinded Placebo (N=2)	---	---	---	---	---	---	---
25-40 mg (N=16)	4 (25.0)	2 (12.5)	2 (12.5)	2 (12.5)	2 (12.5)	2 (12.5)	2 (12.5)
75-125 mg (N=50)	4 (8.0)	3 (6.0)	---	---	1 (2.0)	2 (4.0)	---
Open-label 100-150 mg (N=62)	---	---	---	---	---	---	---
Nausea							
Blinded Placebo (N=10)	4 (40.0)	1 (10.0)	1 (10.0)	---	1 (10.0)	---	---
25-40 mg Blinded (N=21)	2 (9.5)	3 (14.3)	3 (14.3)	1 (4.8)	1 (4.8)	---	---
75-125 mg Blinded (N=74)	16 (21.6)	13 (17.6)	10 (13.5)	6 (8.1)	7 (9.5)	5 (6.8)	4 (5.4)
Open-label 100-150 mg (N=78)	12 (15.4)	4 (5.1)	10 (12.8)	6 (7.7)	6 (7.7)	1 (1.3)	1 (1.3)
Need More Sleep							
Blinded Placebo (N=10)	3 (30.0)	2 (20.0)	1 (10.0)	2 (20.0)	2 (20.0)	2 (20.0)	2 (20.0)
25-40 mg Blinded (N=21)	4 (19.0)	5 (23.8)	3 (14.3)	5 (23.8)	4 (19.0)	5 (23.8)	4 (19.0)
75-125 mg Blinded (N=74)	18 (24.3)	25 (33.8)	13 (17.6)	15 (20.3)	9 (12.2)	8 (10.8)	4 (5.4)
Open-label 100-150 mg (N=78)	22 (28.2)	20 (25.6)	19 (24.4)	15 (19.2)	15 (19.2)	12 (15.4)	7 (9.0)
Nystagmus							
Blinded Placebo (N=10)	---	---	---	---	---	---	---
25-40 mg Blinded (N=21)	---	---	---	---	---	---	---
75-125 mg Blinded (N=74)	---	---	---	---	---	---	---
Open-label 100-150 mg (N=78)	---	---	---	---	---	---	---
Parasthesia							
Blinded Placebo (N=10)	---	---	---	---	---	---	---
25-40 mg Blinded (N=21)	---	---	---	---	---	---	---
75-125 mg Blinded (N=74)	1 (1.4)	1 (1.4)	---	1 (1.4)	---	1 (1.4)	1 (1.4)
Open-label 100-150 mg (N=78)	---	1 (1.3)	2 (2.6)	1 (1.3)	1 (1.3)	---	---

Perspiration							
Blinded Placebo (N=10)	2 (20.0)	---	---	---	---	---	---
25-40 mg Blinded (N=21)	1 (4.8)	---	1 (4.8)	---	---	---	---
75-125 mg Blinded (N=74)	3 (4.1)	---	1 (1.4)	---	---	---	---
Open-label 100-150 mg (N=78)	3 (3.8)	4 (5.1)	1 (1.3)	---	1 (1.3)	1 (1.3)	---
Restlessness							
Blinded Placebo (N=10)	---	---	---	---	---	---	---
25-40 mg Blinded (N=21)	3 (14.3)	1 (4.8)	1 (4.8)	---	2 (9.5)	1 (4.8)	---
75-125 mg Blinded (N=74)	8 (10.8)	6 (8.1)	4 (5.4)	6 (8.1)	5 (6.8)	7 (9.5)	3 (4.1)
Open-label 100-150 mg (N=78)	1 (1.3)	2 (2.6)	2 (2.6)	3 (3.8)	2 (2.6)	---	---
Ruminations							
Blinded Placebo (N=10)	3 (30.0)	1 (10.0)	1 (10.0)	---	---	1 (10.0)	1 (10.0)
25-40 mg Blinded (N=21)	2 (9.5)	1 (4.8)	3 (14.3)	3 (14.3)	2 (9.5)	1 (4.8)	1 (4.8)
75-125 mg Blinded (N=74)	7 (9.5)	11 (14.9)	12 (16.2)	5 (6.8)	8 (10.8)	10 (13.5)	6 (8.1)
Open-label 100-150 (N=78)	6 (7.7)	6 (7.7)	7 (9.0)	2 (2.6)	3 (3.8)	2 (2.6)	1 (1.3)
Sensitivity to Cold							
Blinded Placebo (N=10)	---	---	---	---	---	---	---
25-40 mg Blinded (N=21)	2 (9.5)	---	---	---	1 (4.8)	1 (4.8)	---
75-125 mg Blinded (N=74)	3 (4.1)	3 (4.1)	3 (4.1)	3 (4.1)	1 (1.4)	1 (1.4)	---
Open-label 100-150 mg (N=78)	4 (5.1)	1 (1.3)	1 (1.3)	2 (2.6)	1 (1.3)	1 (1.3)	1 (1.3)
Thirst							
Blinded Placebo (N=10)	---	---	---	---	---	---	---
25-40 mg Blinded (N=21)	1 (4.8)	---	---	---	---	---	---
75-125 mg Blinded (N=74)	5 (6.8)	1 (1.4)	1 (1.4)	1 (1.4)	---	---	---
Open-label 100-150 mg (N=78)	---	1 (1.3)	---	---	---	---	---
Weakness							
Blinded Placebo (N=10)	---	---	---	---	---	---	---
25-40 mg Blinded (N=21)	1 (4.8)	2 (9.5)	---	---	---	---	---
75-125 mg Blinded (N=74)	3 (4.1)	7 (9.5)	4 (5.4)	2 (2.7)	4 (5.4)	2 (2.7)	2 (2.7)
Open-label 100-150 mg (N=78)	9 (11.5)	1 (1.3)	4 (5.1)	1 (1.3)	---	1 (1.3)	---

[a] Diarrhea, impaired judgment, and muscle tension were added based on observations from early studies to reactions list. B Spontaneously reported reactions were not collected fur studies MP16 and MP17. Severe reactions on Day 7=25-40 mg; fatigue (n=2, 9.5%), insomnia (n=2, 9.5%); 75-125 mg anxiety (n=1, 1.4%), low mood (n=2. 2.7%), muscle tension (n=1, 1.4%), nausea (n=1, 1.4%). Listing on day 7 does not necessary mean listed as present or severe on previous days.

In summary, most reactions were not long-lasting in PTSD studies, nor did they warrant cause for clinical concern. Elevations in anxiety and poor sleep were managed across dose groups with short-acting low dose benzodiazepine, or sleep aids as needed, per clinical judgment of the study physician. SRRs were typically observed during drug administration and most were transient and diminished as the drug was metabolized and excreted over a period of 24 hours with the majority of reactions resolving within several days and up to 1 week after dosing. Given the benign safety profile and positive efficacy signal, the sponsor concluded that the risk-benefit analysis of MDMA-assisted psychotherapy weighs in favor of expanding trials to enroll a larger number of participants in placebo-controlled Phase 3 trials to continue evaluation of safety versus efficacy for this treatment.

In the Phase 1/Phase 2 study MPVA-1, among six dyads consisting of one participant diagnosed with PTSD, along with their concerned significant others (CSO), the most common spontaneously reported reactions during open-label Experimental Sessions were lack of appetite (83.3% PTSD and 83.3% CSO participants), anxiety (83.3% PTSD and 66.7% CSO participants), headache (83.3% PTSD and 50.0% CSO participants), and tight jaw (50.0% PTSD and 66.7% CSO participants). During the 7 days following open-label Experimental Sessions, at least half of either PTSD or CSO participants reported fatigue (up to 100.0%), headache (up to 83.3%), lack of appetite (up to 83.3%), anxiety (up to 66.7%), insomnia (up to 66.7%), and nausea (up to 50.0%). Fatigue (50.0%) was the most commonly reported reaction that lasted to Day 7 but only among participants with PTSD. Anxiety (33.3%), lack of appetite (33.3%), and nausea (33.3%) were also reported on Day 7, and again, only among participants with PTSD. Overall, few participants reported any reactions later in the week, which suggests most reactions were short-term and self-limiting.

Spontaneous Reactions in Anxiety Associated with Life-threatening Illness

Spontaneously reported reactions were collected in a sample of 18 participants in MAPS' Phase 2 study MDA-1 during blinded and open-label sessions with inactive placebo or 125 mg MDMA and a supplemental half-dose. Prevalence of reactions is displayed based on number of participants reporting the reaction at least once (Appendix Table 18).

The most commonly reported reactions for the active dose groups were tight jaw /jaw clenching (84.6% in 125 mg blinded sessions versus 20.0% in inactive placebo sessions), thirst (84.6% in 125 mg blinded sessions versus 40.0% in inactive placebo sessions), perspiration (69.2% in 125 mg sessions versus none in placebo sessions, dry mouth (69.2% in 125 mg blinded sessions versus 20.0% in inactive placebo sessions), and headache (61.5% in 125 mg MDMA versus 20.0% placebo). The only severely rated reaction for participants in MDA-1 was a single report of diarrhea recorded during the second day of contact (Day 2) in the 125 mg open-label Stage 2, which was assumed to be related. Due to temporal proximity to dosing, relationship to drug cannot be ruled out. Owing to the very small sample size, it is difficult to draw firm conclusions concerning frequency of spontaneously reported reactions in this sample.

Comparing blinded session active dose with placebo controls during the 7-day safety window (Appendix Table 19), the most commonly reported reactions were fatigue (up to 92.3% in active dose versus 40.0% for inactive placebo), insomnia (up to 46.2% in active dose versus 40.0% in inactive placebo), need more sleep (up to 46.2% in active dose versus 20.0% of inactive placebo), and drowsiness (up to 30.8% in active dose versus 20.0% in inactive placebo). During the 7-day follow-up period after Experimental Sessions, participants most commonly reported headache (up to 46.2% in active dose versus 40.0% in inactive placebo) and anxiety (up to 30.8% of active dose participants versus 40.0% of inactive placebo). In most cases, number of spontaneously reported reactions declined across days of contact.

In summary, spontaneously reported reactions reported in this small sample of participants with anxiety associated with a life-threatening illness receiving 125 mg MDMA were similar to those reported in participants with PTSD. Most of these reactions were resolved by day 7 after drug administration, and were almost entirely of mild to moderate intensity, with only a single report of a severe reaction (diarrhea).

Spontaneous Reactions in Social Anxiety in Autistic Adults

Spontaneously reported reactions were collected in a sample of 12 individuals within MAPS' study MAA-1 (Appendix Table 17). Participants in this study received inactive placebo or ascending doses, with the first session being either 75 or 100 mg MDMA and the second session being 100 or 125 mg MDMA or 100 and 125 mg; participants in Stage 2 all received 75 mg in Session 1 and 125 mg in Session 2. No supplemental dose was administered in this study. Prevalence of reactions is displayed based on number of participants reporting the reaction at least once.

The most commonly reported SRRs were anxiety (75.0% of those receiving 75 to 125 mg in blinded sessions and 25.0% of those receiving 75 to 125 mg in open-label sessions versus 25.0% in inactive placebo sessions), lack of appetite (37.5% of those receiving 75 to 125 mg in blinded sessions and 75.0% of those receiving 75 to 125 mg in open-label sessions versus 25% in inactive placebo sessions), and difficulty concentrating (62.5% in 75 to 125 mg blinded sessions, 50% in 75 to 125 mg open-label sessions versus 25% inactive placebo). Additionally, at least 50% of participants in either the 75 to 125 mg blinded sessions or 75 to 125 mg open-label sessions reported fatigue (vs. 25.0% inactive placebo), headache (vs. 25.0% inactive placebo), muscle tension (vs. 25.0% inactive placebo), perspiration (vs. 25.0% inactive placebo), rumination (vs. 0% in inactive placebo), and sensitivity to cold (0% inactive placebo). The only severe spontaneously reported reaction in this sample was a single report of headache in a participant in the 75 to 125 mg group on the first day of contact.

Most commonly reported SRRs among participants on the autism spectrum with social anxiety during the 7 days after Experimental Sessions was fatigue (up to 75.0% in the 75 to 125 mg groups versus 50.0% in the inactive placebo group) (Appendix Table 17). Low mood (up to 50.0% in the 75 to 125 mg groups vs. 50.0% in the inactive placebo group), headache (up to 37.5% in the 75 to 125 mg groups vs. 25.0% in the inactive placebo group), difficulty concentrating (up to 37.5% in the 75 to 125 mg blinded group vs. 0% in the inactive placebo group), and lack of appetite (up to 37.5% in the 75 to 125 mg

blinded group vs. 0% in the inactive placebo group) were also reported. This sample reported experiencing fewer reactions during the 7-day period than participants with PTSD; there were no reports of diarrhea, impaired gait, or nausea. However, the sample consisted of 12 participants, and a slightly lower dose of 75 mg was used in blinded and open-label sessions. Spontaneously reported reactions after 75 to 125 mg MDMA in autistic adult participants with social anxiety were also mild to moderate and transient, which was similar to other studies conducted for treatment of different indications.

Summary of Spontaneous Reactions Across Indications

In summary, commonly reported acute and sub-acute reactions to MDMA are generally well-tolerated and are rarely reported after the 24-hour period beyond drug administration. Reports of reactions grow increasingly rare after the third day of contact.

6.4.1.3 Adverse Events Summary

Adverse Events in PTSD Studies

Frequency of AEs among participants with PTSD treated with MDMA at any dose across MAPS-sponsored studies conducted under U.S. IND are summarized in Table 10. These studies included MP4, MP8, MP9, MP12, MP16, MP17, and MPVA-1. Adverse events were collected throughout the treatment period and post-treatment (up to 12-month long-term follow-up).

In this sample, participants most frequently reported anxiety and fatigue across treatment groups. Anxiety was reported among 20.0% (n=2) of the placebo group participants, 14.3% (n=2) of the blinded 25-40 mg group participants, 17.6% (n=13) of the blinded 75-125 mg group participants, and 19.7% (n=23) of the open-label 80-150 mg group participants; fatigue was reported among 20.0% (n=2), 19.0% (n=4), 8.1% (n=6), and 13.7% (n=16) of participants, respectively. There were 3 reports of anxiety (3.1%) and no reports of fatigue at long-term follow-up to indicate that fatigue and most reports of anxiety occurred during the treatment period. In the comparator and active dose MDMA groups, > 5% of all participants reported having a headache: 9.5% (2 of 21 participants) in the blinded 25-40 mg, 6.8% in the blinded 75-125 mg (5 of 74 participants), and 23.1% (27 of 117 participants) in the open-label 80-150 mg group; and there were no reports of headache in the placebo group. Sample sizes in both the placebo and comparator blinded 25-40 mg MDMA groups however were relatively low to adequately compare against the active MDMA groups. Therefore, it is unclear whether occurrence of headache might be linked to MDMA treatment. However, there were no reports of headache across all treatment groups at long-term follow-up.

Greater than 5% of both blinded and open-label active MDMA dose group participants reported muscle tightness (9.5% vs. 17.1%, respectively) and nausea (5.4% vs. 12.8%, respectively). There was only one other report of muscle tightness in the placebo group and no other reports of nausea in any other treatment groups. No participant reported headache or nausea at the long-term follow-up. An AE that was most prevalent in the blinded 75-125 mg MDMA group was irritability (5.4%). In comparison, there was only one other report of irritability, which occurred in the open-label 80-150 mg MDMA

group (0.9%). There were no reports of irritability at long-term follow-up. In contrast, there were a few AE's that were more prevalent in the open-label 80-150 mg MDMA dose group vs. the 75-125 mg MDMA group; these AEs included upper respiratory infection (7.7% vs. 1.4%, respectively), decreased appetite (6.8% vs. 1.4%, respectively), and insomnia (14.5% vs. 2.7%, respectively). AEs that were completely unique to the open-label 80-150 mg MDMA dose group included palpitations (5.1%), myalgia (6.8%), nystagmus (6.8%), and suicidal ideation (10.3%). None of these AEs were reported at long-term follow-up.

The main differences between the active blinded and open-label sessions was unblinding of drug and the duration of time in treatment. Specifically, by the time participants were in open-label Experimental Sessions, they would have already had several psychotherapy sessions prior to active treatment. It is possible that having both the inactive and open-label active MDMA-assisted psychotherapy sessions, compared to only 2-3 Experimental Sessions in the blinded active MDMA treatment group, generated more AEs. For example, psychotherapy involves reexamining traumatic experiences, and over the course of several months, this could have triggered mood-related symptoms such as decreased appetite, insomnia, and/ or suicidal ideation. The stress and endurance from prolonged treatment could have compromised participants' immune systems that placed them at higher risk for illness such as an upper respiratory infection. In summary, the AEs that were characteristic of the open-label 80-150 mg MDMA group were likely a consequence of prolonged treatment rather than having an active dose of MDMA.

Table 10: Adverse Events by Body System Organ Class (MedDRA 17.1) At Any Severity among Participants with PTSD in Sponsor-Supported Phase 2 Studies of MDMA-Assisted Psychotherapy

SOC	Adverse Event Preferred Term	Placebo 0 mg	Blinded 25-40 mg	Blinded 75-125 mg	Open-label 80-150 mg	Long-Term Follow-up[C]
Subjects per Dose Group		10	21	74	117[A]	97
Participants who reported at least 1 AE		9	11	55	96	10
		N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Cardiac disorders						
	Palpitations	---	---	---	6 (5.1)	---
	Sinus tachycardia	---	---	1 (1.4)	---	---
	Ventricular extrasystoles	---	---	---	1 (0.9)	---
Ear and labyrinth disorders						
	Ear discomfort	---	---	---	1 (0.9)	---
	Tinnitus	---	1 (4.8)	1 (1.4)	1 (0.9)	---
Endocrine disorders						
	Hypothyroidism	---	1 (4.8)	1 (1.4)	---	1 (1.0)
Eye disorders						
	Altered visual depth perception	---	---	---	1 (0.9)	
	Dry Eye	---	---	---	1 (0.9)	---
	Ocular discomfort	---	---	---	1 (0.9)	---
	Photophobia	---	---	---	1 (0.9)	---
	Vision blurred	---	---	1 (1.4)	3 (2.6)	---
	Visual impairment	---	---	5 (6.8)	4 (3.4)	---

	Vitreous floaters	---	---	1 (1.4)	---	---
Gastrointestinal disorders						
	Abdominal discomfort	---	---	---	5 (4.3)	---
	Abdominal pain	---	---	2 (2.7)	2 (1.7)	---
	Abdominal pain, upper	1 (10.0)	---	---	---	---
	Anal fissure	---	---	---	1 (0.9)	---
	Aphthous ulcer	---	---	---	1 (0.9)	---
	Constipation	---	---	1 (1.4)	---	---
	Diarrhea	---	1 (4.8)	4 (5.4)	4 (3.4)	---
	Dyspepsia	---	---	1 (1.4)	1 (0.9)	---
	Dry Mouth	---	---	---	2 (1.7)	---
	Eructation	---	---	---	1 (0.9)	---
	Food poisoning	---	---	---	1 (0.9)	---
	Gastric Ulcer	---	---	---	1 (0.9)	---
	Intestinal obstruction	---	---	1 (1.4)	---	---
	Irritable Bowel Syndrome	---	---	---	1 (0.9)	---
	Nausea	---	---	4 (5.4)	15 (12.8)	---
	Oropharyngeal blistering	---	---	1 (1.4)	---	---
	Tongue discomfort				1 (0.9)	
	Vomiting	---	---	5 (6.8)	3 (2.6)	---
General disorders and administrative site conditions						
	Asthenia	---	---	1 (1.4)	1 (0.9)	---
	Chest discomfort				2 (1.7)	---
	Chills	---	---	---	2 (1.7)	---
	Cyst	---	---	---	1 (0.9)	---
	Fatigue	2 (20.0)	4 (19.0)	6 (8.1)	16 (13.7)	---
	Facial pain	1 (10.0)	---	---	---	---
	Feeling abnormal	---	---	1 (1.4)	---	---
	Feeling hot	---	---	2 (2.7)	1 (0.9)	---
	Feeling cold	---	---	---	1 (0.9)	---
	Feeling of body temperature change	---	---	---	1 (0.9)	---
	Gait disturbance	---	---	---	1 (0.9)	---
	Hangover	---	---	---	1 (0.9)	---
	Influenza-like illness	---	---	1 (1.4)	---	---
	Malaise	---	---	1 (1.4)	---	---
	Oedema peripheral	---	---	---	1 (0.9)	---
	Pain	1 (10.0)	2 (9.5)	2 (2.7)	4 (3.4)	---
	Pyrexia	---	1 (4.8)	2 (2.7)	4 (3.6)	---
	Temperature intolerance	---	---	---	2 (1.7)	---
Infections and infestations						
	Acute sinusitis	---	---	---	1 (0.9)	---
	Angina tonsils	---	---	---	1 (0.9)	---
	Appendicitis	---	---	---	---	1 (1.0)
	Conjunctivitis	---	---	---	1 (0.9)	---
	Hordeolum	---	1 (4.8)	---	---	---
	Infected cyst	---	---	---	1 (0.9)	---
	Influenza	---	2 (9.5)	2 (2.7)	---	---
	Laryngitis	---	---	1 (1.4)	---	---
	Nasopharyngitis	---	---	---	1 (0.9)	---
	Otitis Media	1 (10.0)	1 (4.8)	---	---	---

	Pharyngitis	1 (10.0)	---	---	---	---
	Pharyngitis, streptococcal	---	---	1 (1.4)	---	---
	Pneumonia	---	---	1 (1.4)	2 (1.7)	---
	Pneumonia, chlamydia	---	---	1 (1.4)	---	---
	Sinusitis	---	1 (4.8)	2 (2.7)	1 (0.9)	---
	Tinea pedis	---	---	---	1 (0.9)	---
	Tooth abscess	---	1 (4.8)	---	---	---
	Tooth infection					1 (1.0)
	Upper respiratory tract infection	1 (10.0)	---	1 (1.4)	9 (7.7)	---
	Urethritis	---	---	---	---	1 (1.0)
	Urinary tract infection	---	---	1 (1.4)	2 (1.7)	---
	Vaginal infection	---	---	1 (1.4)	---	---
	Viral upper respiratory infection	---	---	---	3 (2.6)	---
Immune system disorders						
	Hypersensitivity	---	---	---	1 (0.9)	---
Injury, poisoning, procedural complications						
	Arthropod bite	---	---	---	1 (0.9)	---
	Concussion	---	---	---	1 (0.9)	1 (1.0)
	Contusion	---	---	2 (2.7)	2 (1.7)	---
	Corneal abrasion	---	---	---	1 (0.9)	---
	Fracture	---	---	---	1 (0.9)	---
	Exposure to violent event	---	---	---	1 (0.9)	---
	Head injury	---	---	---	1 (0.9)	---
	Incision site pain	---	---	---	1 (0.9)	---
	Incorrect dose administered	---	---	1 (1.4)	---	---
	Intentional product misuse [of a concomitant medication]	---	---	---	1 (0.9)	---
	Joint dislocation	---	---	---	1 (0.9)	---
	Laceration	---	---	---	2 (1.7)	---
	Ligament sprain	---	1 (4.8)	---	2 (1.7)	---
	Limb injury	---	---	1 (1.4)	---	---
	Lower limb fracture	---	---	1 (1.4)	---	---
	Post-concussion syndrome	---	---	---	---	1 (1.0)
	Procedural nausea	---	---	---	1 (0.9)	---
	Road traffic accident	1 (10.0)[B]	---	---	---	1 (1.0)
	Skeletal injury	---	---	1 (1.4)	---	---
	Skin abrasion	---	---	1 (1.4)	---	---
	Sunburn	---	---	---	1 (0.9)	---
	Thermal burn	---	---	---	1 (0.9)	---
	Wound	---	---	---	1 (0.9)	---
Investigations						
	Body temperature fluctuations	---	---	---	1 (0.9)	---
	Red blood cell sedimentation rate increased	---	---	---	---	1 (1.0)
	Weight decreased	---	---	---	1 (0.9)	---

Metabolism and nutrition disorders						
	Anorexia	---	---	1 (1.4)	---	---
	Decreased appetite	---	---	1 (1.4)	8 (6.8)	---
	Dehydration	---	---	---	1 (0.9)	---
	Iron deficiency anemia	---	---	---	1 (0.9)	---
	Vitamin D deficiency	---	1 (4.8)	---	---	---
Musculoskeletal and connective tissue disorders						
	Arthralgia	1 (10.0)	---	---	2 (1.7)	---
	Back pain	1 (10.0)	---	2 (2.7)	4 (3.4)	---
	Clavicle fracture	---	---	1 (1.4)	---	---
	Joint stiffness	---	---	---	2 (1.7)	---
	Muscle spasms	1 (10.0)	---	2 (2.7)	1 (0.9)	---
	Muscle strain	---	---	---	1 (0.9)	---
	Muscle tightness	1 (10.0)	---	7 (9.5)	20 (17.1)	---
	Muscle twitching	---	---	1 (1.4)	---	---
	Muscular weakness	---	---	---	1 (0.9)	---
	Musculoskeletal chest pain	1 (10.0)	---	---	---	---
	Musculoskeletal pain	---	---	2 (2.7)	2 (1.7)	---
	Musculoskeletal stiffness	---	---	---	3 (2.6)	---
	Myalgia	---	---	---	8 (6.8)	---
	Neck pain	1 (10.0)	---	---	5 (4.3)	---
	Pain in extremity	---	---	---	3 (2.6)	---
	Pain in jaw				4 (3.4)	---
	Plantar fasciitis	---	---	---	1 (0.9)	---
	Synovitis				1 (0.9)	---
	Trismus	---	---	---	1 (0.9)	---
Neoplasms benign, malignant and unspecified						
	Breast cancer stage 1	---	---	---	1 (0.9)	---
	Metastases to central nervous system	---	---	---	---	1 (1.0)
	Neuroma	---	---	---	1 (0.9)	---
Nervous system disorders						
	Burning sensation	1 (10.0)	---	1 (1.4)	1 (0.9)	---
	Disturbance in attention	---	---	---	2 (1.7)	
	Dizziness	---	---	3 (4.1)	9 (7.7)	---
	Dysgeusia	---	---	---	2 (1.7)	---
	Exaggerated startle response				1 (0.9)	
	Headache	---	2 (9.5)	5 (6.8)	27 (23.1)	---
	Hypoaesthesia	---	---	---	1 (0.9)	---
	Hypoaesthesia facial	---	---	1 (1.4)	---	---
	Hypersomnia	---	1 (4.8)	---	3 (2.6)	---
	Migraine	---	1 (4.8)	---	1 (0.9)	---
	Muscular contractions involuntary	---	---	---	1 (0.9)	---
	Myoclonus	---	---	1 (1.4)	---	---
	Neuritis	---	---	---	1 (0.9)	---
	Nystagmus	---	---	---	8 (6.8)	---
	Paresthesia	---	---	1 (1.4)	4 (3.4)	---
	Restless legs syndrome	---	---	---	1 (0.9)	---
	Sciatica	1 (10.0)	---	---	---	---
	Syncope (postural)	---	---	1 (1.4)	3 (2.6)	---

	Tension headache	---	---	1 (1.4)	1 (0.9)	---
	Tremor	---	---	---	3 (2.6)	---
Psychiatric disorders						
	Aggression	---	---	---	1 (0.9)	---
	Agitation	---	---	---	1 (0.9)	---
	Anger	---	---	---	1 (0.9)	---
	Anxiety	2 (20.0)	2 (9.5)	13 (17.6)	23 (19.7)	3 (3.1)
	Bruxism	---	---	2 (2.7)	4 (3.4)	---
	Confusional state	---	---	---	1 (0.9)	---
	Conversion disorder	---	---	---	1 (0.9)	---
	Depressed mood	1 (10.0)	2 (9.5)	8 (10.8)	4 (3.4)	---
	Depression	---	---	1 (1.4)	1 (0.9)	2 (2.1)
	Derealization	---	---	1 (1.4)	1 (0.9)	---
	Dermatillomania	---	---	---	1 (0.9)	---
	Dissociation	1 (10.0)	1 (4.8)	1 (1.4)	---	---
	Disturbance in attention	---	---	3 (4.1)	---	---
	Emotional disorder	---	---	---	1 (0.9)	---
	Emotional distress	1 (10.0)	1 (4.8)	1 (1.4)	---	---
	Fear of eating	---	---	---	1 (0.9)	---
	Feelings of worthlessness	---	---	---	1 (0.9)	---
	Flashback	1 (10.0)	---	1 (1.4)	3 (2.6)	---
	Grief reaction	---	---	---	1 (0.9)	---
	Hypnagogic hallucination	---	---	---	1 (0.9)	---
	Hypnopompic hallucination	---	---	---	1 (0.9)	---
	Initial insomnia	---	---	---	1 (0.9)	---
	Insomnia	1 (10.0)	1 (4.8)	2 (2.7)	17 (14.5)	---
	Intentional self-injury	1 (10.0)	1 (4.8)	---	1 (0.9)	1 (1.0)
	Intrusive thoughts	---	---	---	1 (0.9)	---
	Irritability	---	---	4 (5.4)	1 (0.9)	---
	Major depression	---	---	1 (1.4)	---	1 (1.0)
	Memory impairment	1 (10.0)	---	---	---	---
	Negative thoughts	---	1 (4.8)	---	---	---
	Nightmare	---	---	---	3 (2.6)	---
	Obsessive rumination	---	---	2 (2.7)	1 (0.9)	---
	Obsessive thoughts	---	---	---	1 (0.9)	
	Panic attack	---	---	3 (4.1)	1 (0.9)	1 (1.0)
	Panic reaction	---	---	---	2 (1.7)	---
	PTSD	---	---	---	1 (0.9)	---
	Restlessness	---	---	2 (2.7)	2 (1.7)	---
	Somatoform disorder	---	---	1 (1.4)	---	---
	Somnolence	---	---	1 (1.4)	---	---
	Suicidal ideation	---	1 (4.8)	1 (1.4)	12 (10.3)	2 (2.1)
	Suicide attempt	---	---	---	1 (0.9)	
	Tension	---	---	1 (1.4)	---	---
	Tic	---	---	1 (1.4)	1 (0.9)	---
	Time perception altered	---	1 (4.8)	---	---	---
	Trichotillomania	---	1 (4.8)	---	---	---
Renal and urinary disorders						
	Dysuria	---	---	1 (1.4)	1 (0.9)	---
	Micturition urgency	---	---	---	2 (1.7)	---
	Nocturia	---	---	1 (1.4)	---	---

	Urinary retention				2 (1.7)	
Reproductive disorders						
	Dysmenorrhoea	---	---	---	1 (0.9)	---
	Menorrhagia	---	---	---	1 (0.9)	---
	Menstruation irregular	---	---	---	1 (0.9)	---
	Ovarian Cyst	---	---	1 (1.4)	---	1 (1.0)
	Ovarian cyst ruptured	---	---	---	---	1 (1.0)
Respiratory, thoracic and mediastinal disorders						
	Asthma	---	---	---	1 (0.9)	---
	Cough	---	1 (4.8)	---	1 (0.9)	---
	Dyspnea	---	---	2 (2.7))	2 (1.7)	---
	Nasal congestion	---	1 (4.8)	---	1 (0.9)	---
	Oropharyngeal pain	---	---	1 (1.4)	4 (3.4)	---
	Sinus headache	---	---	1 (1.4)	---	---
	Throat tightness	1 (10.0)	---	---	---	---
Skin and subcutaneous tissue disorders						
	Acne	---	---	---	1 (0.9)	---
	Dermatitis	1 (10.0)	---	---	---	---
	Erythema	---	---	---	1 (0.9)	---
	Hyperhidrosis	---	---	---	4 (3.4)	---
	Night sweats	---	---	---	1 (0.9)	---
	Petechiae	---	---	1 (1.4)	---	---
	Photosensitivity reaction	---	---	---	1 (0.9)	---
	Pruritis	1 (10.0)	---	---	2 (1.7)	---
	Pseudofolliculitis barbae	---	---	1 (1.4)	---	---
	Psoriasis	---	---	1 (1.4)	---	---
	Urticaria	---	1 (4.8)	---	---	---
Social circumstances						
	Substance Use	---	---	---	1 (0.9)	---
Surgical and medical procedures						
	Foot operation	---	---	1 (1.4)	---	---
Vascular disorders						
	Hypertension	---	---	1 (1.4)	---	---
	Deep vein thrombosis	---	---	1 (1.4)	---	---
	Orthostatic hypotension	---	---	---	1 (0.9)	---
	Peripheral coldness	---	---	---	2 (1.7)	---

[a] The 24-27 events collected separately as "spontaneously reported reactions in studies MP1-MP12 were collected as adverse events in this manner for studies MP16 and MP17. Absence of these events blinded studies / times may occur because these events were reported as spontaneously reported reactions. See Table 8 and Table 9.

[b] A previously uncoded event in a previous study ("passenger in traffic accident, no injury") has been upversioned to "road traffic accident".

[c] Participants in MPVA1 (N=6) had a 6-month follow-up. All other participants had a 12-month or more follow-up.

The number of severe adverse events (SAEs) across all treatment groups was relatively low (Table 11). The only SAEs that were reported by more than one participant were depressed mood and panic attack, which occurred in the blinded 75 to 125 mg MDMA group. Neither were reported in the open-label 80 to 150 mg MDMA group or in the long-term follow-up study. At long-term follow-up, there was one report each of severe depression, anxiety, and severe suicidal ideation. The placebo group sample was too

small for adequate comparison across groups. Nonetheless, these data suggest the need for careful monitoring of PTSD participants for such psychiatric disorders throughout the study period irrespective of MDMA dose.

Table 11: Severe Adverse Events by Body System Organ Class (MedDRA 17.1) among Participants with PTSD in Sponsor-Supported Phase 2 Studies of MDMA-Assisted Psychotherapy

SOC	Adverse Event Preferred Term	Placebo 0 mg	Blinded 25-40 mg	Blinded 75-125 mg	Open-label 80-150 mg	Long-Term Follow-up[C]
Subjects per Dose Group		10	21	74	117[A]	97
		N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Gastrointestinal disorders						
	Abdominal pain	---	---	---	1 (0.9)	---
	Anal fissure	---	---	---	1 (0.9)	---
	Intestinal obstruction	---	---	1 (1.4)	---	---
General disorders and administrative site conditions						
	Pain	---	1 (4.8)	---	---	---
Infections and infestations						
	Appendicitis	---	---	---	---	1 (1.0)
	Sinusitis	---	---	1 (1.4)	---	---
Injury, poisoning, procedural complications						
	Concussion	---	---	---	1 (0.9)	---
	Exposure to violent event	---	---	---	1 (0.9)	---
	Lower limb fracture	---	---	1 (1.4)	---	---
Musculoskeletal and connective tissue disorders						
	Musculoskeletal chest pain	1 (10.0)	---	---	---	---
Neoplasms benign, malignant and unspecified						
	Breast cancer stage 1	---	---	---	1 (0.9)	---
Nervous system disorders						
	Headache	---	1 (4.8)	---	1 (0.9)	---
	Migraine	---	1 (4.8)	---	---	---
	Sciatica	1 (10.0)	---	---	---	---
	Syncope (postural)	---	---	---	1 (0.9)	---
Psychiatric disorders						
	Anger	---	---	---	1 (0.9)	---
	Anxiety	---	---	1 (1.4)	---	1 (1.0)
	Depressed mood	---	---	2 (2.7)	---	---
	Depression	---	---	---	---	1 (1.0)
	Flashback	1 (10.0)	---	---	---	---
	Insomnia	---	1 (4.8)	---	---	---
	Major depression	---	---	1 (1.4)	---	---
	Obsessive rumination	---	---	1 (1.4)	---	---
	Panic attack	---	---	2 (2.7)	---	---
	Suicidal ideation	---	1 (4.8)	1 (1.4)	1 (0.9)	1 (1.0)
	Suicide attempt	---	---	---	1 (0.9)	
Reproductive disorders						
	Ovarian cyst ruptured	---	---	---	---	1 (1.0)

Since MDMA is administered as an adjunct to psychotherapy, judging relationships to Investigational Product is a known challenge for this combined therapy. In the context of complex medical histories associated with the PTSD diagnosis, somatic symptoms may wax and wane independent of treatment. In addition, it is known that processing trauma during psychotherapy for PTSD, with or without concomitant pharmacological treatment, can temporarily increase symptoms as an expected aspect of the therapeutic process. This was demonstrated by the high incidence of spontaneously reported reactions and AEs in the placebo group.

Among related AEs reported during and after drug administration, somatic symptoms were more frequently experienced in active dose participants, such as pain associated with body tension, muscle tightness, musculoskeletal pain in the shoulder, back pain, and myalgia. As previously discussed in Section 6.4.1 Adverse Events, it is difficult to judge relationship between Investigational Product and conditions associated with medical history diagnoses. Pain and somatic symptoms can be directly related to traumatic events, such as physical or sexual assault, a motor vehicle accident, or combat [641]. A meta-analytic review and several large studies have found a robust association between PTSD and somatic symptoms, suggesting that PTSD itself may be a contributing factor beyond combat exposure, sexual, or physical abuse that led to the PTSD [642-645].

Although MDMA is not a classic hallucinogen, as classified by chemical structure and mechanism of action, data from sponsor-supported studies suggest MDMA was associated with mild psychedelic effects, such as hypnagogic and hypnopompic hallucinations and visual distortions in some individuals. Hallucinogenic subjective effects were not actively assessed during therapy sessions, as was done in Phase 1 studies of healthy volunteers [18, 21, 22, 646]. Any unsolicited reports of hallucinogenic effects were collected as AEs in sponsor-supported studies.

Special Report on MDMA-assisted Psychotherapy and Covid-19

The advent of the Covid-19 pandemic has necessitated a closer examination of any potential links between MDMA-assisted psychotherapy and increased risk of contracting the virus. In Phase 2 studies, among PTSD participants, a total of 9.4% (10 of 106) participants reported an upper respiratory tract infection (URTI) that had occurred within 20 days after an active MDMA-assisted session (Table 12). [Note: In Section 6.4.1.3 Adverse Events Summary, URTI was reported by blinded 75 to 125 mg vs. open-label treatment groups.] Two participants reported an URTI that occurred more than 30 days after an active MDMA-assisted session. One placebo participant, who did not receive any active MDMA, also reported an URTI 3 days following an inactive dose. The sample consisted of participants from both blinded and open-label active MDMA groups without adequate controls for comparisons. Therefore, although unlikely, it remains unclear whether reports of URTI might be specifically linked to active MDMA. There is evidence from multiple epidemiologic studies to suggest that having a stress-related disorder, including PTSD, were associated with higher risk of infections, with hazard ratios ranging from 1.47 (95% CI: 1.37, 1.58) [647] to 1.8 (95% CI: 1.6, 2.0) [648]. Therefore, even without any treatment, PTSD participants might be at increased risk of infections that could include Covid-19. However, at present, there is no evidence to suggest MDMA-assisted psychotherapy would increase these risks.

Table 12: Upper Respiratory Tract Infections among Participants with PTSD in Sponsor-Supported Phase 2 Studies of MDMA-Assisted Psychotherapy

	Study	Subject	# Days Since Last Dosing	MDMA Dose (mg)	Serious/ Severe	Treatment Action	Relationship[2]
0-20 days Post-dose	MP1	0102	3	.	No/ Moderate	Non-Rx Medication	Possibly
	MP1	0206	14	125	No/ Moderate	Procedure/ therapy	Possibly
	MP1	0217	4	125+62.5[1]	No/ Moderate	Non-Rx Medication	Possibly
	MP1	0220	3	125+62.5	No/ Moderate	Procedure/ therapy	Possibly
	MP9	9001	5	125+62.5	No/ Mild	Non-Rx Medication	Not related
	MPVA1	1002	3	75+37.5	No/ Moderate	.	Possibly
	MPVA1	1005	4	100+50	No/ Mild	.	Possibly
	MP16	1602002	16	120+60	No/ Mild	Non-Rx Medication	n/a
	MP16	1610004	4	80+40	No/ Mild	Non-Rx Medication	n/a
			20	120+60	No/ Moderate	Non-Rx Medication	n/a
	MP16	1611005	14	80+40	No/ Mild	Non-Rx Medication	n/a
	MP17	1713003	5	100+50	No/ Mild	None	n/a
			16	125+62.5	No/ Moderate	None	n/a
> 30 days Post-dose	MP1	0216	45	125+62.5[1]	No/ Moderate	Hospitalization	Not related
	MP16	1611002	58	120+60	No/ Mild	Non-Rx Medication	n/a

[1] MP1 participant - placebo, URTI occurred in open-label
[2] MP16 and MP17: per protocol relationship was not collected and will be derived in analysis

Adverse Events in Social Anxiety in Autistic Adults

In autistic adult participants with social anxiety (MAA-1), the frequency of any given AE in each study group was less than 25% (or 1 to 2 participants). The majority of AEs were psychiatric disorders (ten in active dose groups and two in the inactive placebo group), followed by infections and infestations (three in active dose groups and two in the inactive placebo group) (see Appendix Table 19 for more details). Participants in the blinded 75 to 125 mg group reported the highest proportion of depressed mood (25%) and suicidal ideation (25%). There was no report of depressed mood in the placebo group, although there was one report of depression. There was also one count of suicidal ideation in the placebo group. The occurrence of depressed mood/ depression and suicidal ideation in both blinded placebo and 75 to 125 mg groups suggest these AEs likely occurred independent of drug administration. There were three counts of panic attack/ panic reaction in only active dose groups, which might be attributed to drug administration. There were no severe adverse events reported in the study. However, small sample size warrants further investigation to elucidate relationships between AEs and MDMA-assisted psychotherapy in autistic adults with social anxiety.

Adverse Events in Anxiety Associated with Life-threatening Illness

Adverse events reported during the study of MDMA-assisted psychotherapy in participants with anxiety in response to facing life-threatening disorders (MDA-1) included psychiatric disorders, nervous system disorders, gastrointestinal symptoms, and infections (Appendix Table 20). Of the seven AEs rated as severe, six AEs occurred in a single individual after cancer reoccurrence: meningitis, sepsis, aphasia, cerebrovascular accident, and spinal cord paralysis. The participant's last visit was the Primary Endpoint. The subject died prior to Long-term Follow-up. The other severe AE (invasive ductal breast carcinoma) occurred in a different participant during the long-term follow-up.

Overall, 40.0% of blinded placebo participants, 84.6% of blinded 125 mg participants, and 41.2% of open-label 125 mg participants reported any AE's during Experimental Sessions. The most commonly reported AE was insomnia, which was reported among 20.0% of blinded placebo participants, 15.4% of blinded 125 mg participants, and 23.5% of open-label 125 mg participants. Three counts of fatigue (23.1%) were reported only among blinded 125 mg participants. It may be possible drug administration was linked to insomnia and fatigue, which were also commonly reported AEs in other sponsor-supported study samples. In this sample, apart from insomnia, all other psychiatric AEs were reported by participants in active dose groups. Anxiety was reported in one blinded 125 mg participant and two open-label 125 mg participants, which was expected given the indication under study. There were single reports of bruxism, depressed mood, depression, dissociation, and hypomania in either the blinded 125 mg or open-label 125 mg groups (see Appendix Table 20).

Non-psychiatric AEs with more than one count included influenza (15.4%), contusion (15.4%), and back pain (15.4%), which occurred only among blinded 125 mg participants, although these events were likely unrelated to drug administration. Similarly, there were a total of nine participants, and a total of 16 AEs, that were reported at 12-month follow-up across all study participants. But, given the small sample sizes, it is unlikely that any occurrence of AEs 1 year or more following Experimental Sessions were associated with the study treatment.

One subject in this study experienced a cascade of adverse events, including several SAEs, after completing the course of the main study and prior to or at long-term follow-up that all followed from recurrence of chordoma. This event was expected given the participant's medical history of chordoma. After the recurrence was noted, the subject received one additional Experimental Session. She then underwent debulking surgery, radiation, immunotherapy, and chemotherapy for treatment before significant deterioration (including spinal cord paralysis, spinal meningitis, septicemia, and cerebrovascular accident followed by aphasia and inability to speak) and subsequent death.

It is challenging to make comparisons or draw conclusions about nature or frequency of adverse events in this sample owing to small sample size. Psychiatric AEs in general, and anxiety in particular, are expected in this patient population and with MDMA combined with psychotherapy that encourages confronting emotionally distressing material. It is also expected that participants diagnosed with a life-threatening illness may experience more severe AEs related to their medical history.

6.4.1.4 Serious Adverse Reactions

SARs are serious adverse events possibly or probably related to MDMA administration. Not related serious adverse events are not presented in the IB. See Table 13 below for a summary.

Table 13: Serious Adverse Reactions in Sponsor-Supported Studies of MDMA-Assisted Psychotherapy Across Indications as of April 31, 2020

Dose	Comparator Dose (0-40 mg)	Active Dose (75-125 mg)	Open-label (100-150 mg)
	N	N	N
Cardiovascular			
Ventricular Extrasystoles (exacerbation)	---	---	1

One cardiac SAR has occurred within all sponsor-supported studies to date. In a PTSD study (MP-8), subject 0811 experienced an increase in frequency of ventricular extrasystoles, a form of cardiac arrhythmia, on the day of his third and final Experimental Session with open-label 125 mg MDMA. The subject had no other signs and no symptoms of cardiac distress. In the absence of any symptoms of coronary insufficiency, the investigator judged the only medical measure necessary to be withholding the supplemental dose of MDMA. This was the final drug administration in the open-label

crossover period of the study known as Stage 2. No similar events were detected during the first two 125 mg Experimental Sessions, nor the two blinded Experimental Sessions with 30 mg MDMA in the blinded period of the study known as Stage 1. There was no evidence of acute cardiac damage or ischemia or underlying heart disease. At baseline during screening, the subject had one ventricular extrasystole on the electrocardiogram (EKG), but the EKG was otherwise normal. The subject had a positive family history: his father had a coronary artery bypass graft, which had prompted the subject to consult a cardiologist several years before study enrollment, and the cardiologist's note indicated that he did not suspect cardiovascular disease or see the need for further workup. Based on the medical history and clinical presentation of this subject, the investigator judged the SAR to be a moderate exacerbation probably related to drug administration, although since the subject was under observation when the event was noted, it cannot be determined if the same event occurred undetected prior to MDMA administration while the subject was not being monitored. The event required overnight monitoring in the hospital but did not lead to any adverse sequelae. He was given one dose of 25 mg metoprolol by the hospital physician but did not require any ongoing treatment. Serial cardiac isoenzymes, an echocardiogram and a nuclear stress test performed during the overnight hospital admission failed to show evidence of cardiovascular or other cardiac disease. Full recovery occurred 1 day after MDMA administration. Arrhythmia is described in Sections 4.1.3.2 and 5.1.2 as an expected adverse effect of MDMA.

Adverse Events Summary

Anxiety-related psychiatric symptoms were the most commonly related AEs reported in MAPS supported studies. Most AEs were rated mild or moderate and transient in nature. MDMA produced several expected adverse events, collected as spontaneous reports on the day of an Experimental Session and for 7 days afterwards, with most AEs subsiding before the end of the seven-day period. At least one post-drug AE occurred in nearly every system organ class, with most being general symptoms, nervous system disorders or psychiatric disorders. A single SAR was reported, one cardiac event (increase in frequency of ventricular extrasystoles), that occurred in Study MP-8 as described above. SUSARS were infrequent in the program and the sponsor closely monitors any SUSARs to determine if any should be upgraded to SARs. If any new risks are identified, the IB will be updated with this information accordingly.

6.4.2 Suicidal Ideation and Behavior

There is high incidence of positive suicidal ideation and behavior in populations of people with PTSD, especially those suffering from chronic, treatment-resistant PTSD [649, 650]. The FDA has responded to concerns over the occurrence of treatment emergent suicidal ideation or behavior by requiring clinical trials of psychiatric drugs to measure suicidality via the C-SSRS, a clinician-administered guided interview [651]. Individuals with serious ideation or behavior are to be closely monitored until levels return to normal or additional interventions are recommended by the therapist.

Data on suicidal ideation or behavior was not formally measured in the first two sponsor-supported studies (MP-1 and MP-2). The C-SSRS was added to subsequent studies in

order to monitor suicidal ideation and behavior. The C-SSRS was assessed throughout each study, including lifetime incidence, baseline, before/during/after drug administration, endpoints when other measures were administered, and follow-up visits. In MDMA-assisted psychotherapy, thoughts of suicide may surface due to the nature of the therapeutic method, wherein a person may re-experience emotions associated with the traumatic event and reprocess the memory. However, evidence from clinical studies indicates that these thoughts were more often transient, returned to normal, or even improved following MDMA treatment.

C-SSRS in PTSD Studies

Suicidal ideation and behavior were collected using the C-SSRS and data are reported according to the C-SSRS Scoring and Data Analysis Guide [652]. A positive response for suicidal ideation was counted when a subject responded "yes" to any one of the five suicidal ideation questions (Categories 1 to 5) on the C-SSRS (i.e., a score >0 for suicidal ideation score). Serious suicidal ideation was a suicidal ideation category score of 4 or 5. A positive response for suicidal behavior occurred when a subject responded "yes" to any one of the five suicidal behavior questions (Categories 6 to 10) on the C-SSRS (i.e., a score >0 for suicidal behavior score). Lifetime scores accounted for all suicidal ideation and behavior prior to enrollment according to subject recall and medical records. Pre-drug exposure represents measures collected on the Since Last Visit C-SSRS after enrollment during Preparatory Sessions and before first drug administration in Experimental Session 1 upon completion of tapering off psychiatric medications. Frequencies were presented as subject counts at each time point. When time points covered multiple visits, percentages were based on the number of observations in which participants would have had the opportunity to report.

In studies MP4, MP8, MP9, MP12, MP16, and MP17, the majority of participants reported lifetime prevalence of positive ideation and there were some reports of serious ideation and positive behavior, which was expected among study samples diagnosed with PTSD (Table 14 and Figure 5). At baseline, or Pre-drug Exposure (i.e., in the Preparatory Session prior to Experimental Session 1), compared to lifetime prevalence, there were far fewer reports of positive ideation, no reports of serious ideation, and one report of positive behavior. Overall, participants in the blinded active dose (75 to 125 mg MDMA) and open-label Stage 2 active dose (100 to 125 mg MDMA) groups reported positive ideation throughout the Experimental Sessions at pre-drug, during-drug, and integration days 1, 2, and 7. The prevalence of positive ideations, particularly in the earlier Experimental Session, might have been due to withdrawal symptoms after prescription medications tapering of SSRIs and/ and benzodiazepines [653-655], which was a study eligibility criterion. Additionally, in both the non-drug and active MDMA-assisted psychotherapy sessions, participants were asked to recall and discuss experiences related to their PTSD diagnosis, which could have triggered thoughts of suicidality throughout the Experimental Sessions. Therefore, it is not surprising participants in the blinded active dose (75 to 125 mg MDMA) and open-label Stage 2 active dose (100 to 125 mg MDMA) groups had reported positive ideation throughout the Experimental Sessions.

At post-treatment, following all Experimental Sessions, blinded active dose (75 to 125 mg MDMA) group participants continued to report positive ideation at the Primary or Secondary Endpoint, End of Stage 1 or 2, and Long-term Follow-up: 34.9% (15 of 43 participants), 28.9% (11 of 38 participants), and 27.7% (13 of 47 participants), respectively; and, there were a few reports of serious ideation: 4.7% (2 of 43 participants), 0 (0 of 38 participants), and 2.1% (1 of 47 participants), respectively. In the open-label Stage 2 active dose (100 to 125 mg MDMA) group, 5 participants reported positive ideation at Primary or Secondary Endpoint, 3 participants at End of Stage 1 or 2, and 0 at Long-term Follow-up. Among the placebo group and blinded 25 to 40 mg MDMA group, at any given post-treatment assessment of CSSRS, there were only up to one participant who reported having positive ideation: 1 of 2 participants in the placebo and 1 of 12 to 13 participants in the blinded comparator group; and no reports of serious ideation or positive behavior. In the context of MDMA-assisted psychotherapy, MDMA can modulate consolidation or reconsolidation of fear-related memories [277, 279, 656, 657].

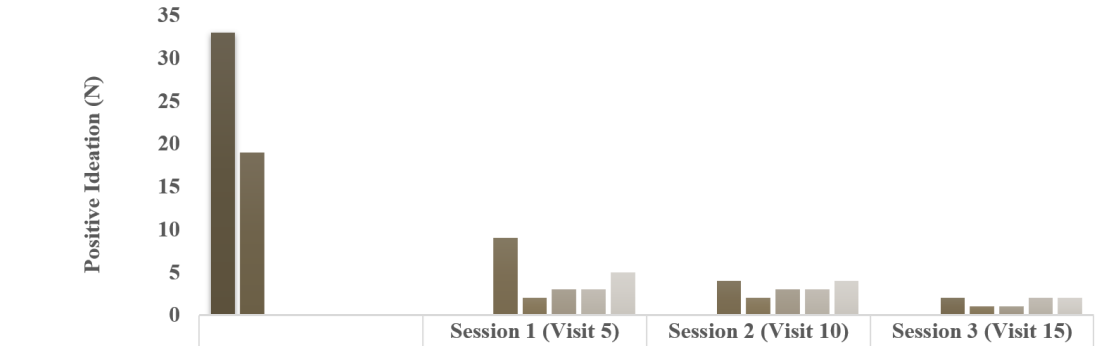
There were no reports of positive behavior across all treatment groups throughout all Experimental Sessions and post-treatment assessment period.

Table 14: C-SSRS Positive and Serious Responses During Screening, Experimental Sessions Including Integrative Sessions, and Post-treatment for PTSD Studies MP-4, MP-8, MP-9, MP12, MP16, MP17 and MPVA-1*

		Screening N (%)	**Session 1 N (%)**	**Session 2 N (%)**	**Session 3 N (%)**	**Post-treatment N (%)**
		Lifetime[a]/ Pre-drug Exposure[b]	Pre-drug[c] / During-drug[d]/ D1/ D2/ D7	Pre-drug[c] / During-drug[d]/ D1/ D2/ D7	Pre-drug[c] / During-drug[d]/ D1/ D2/ D7	1° or 2° Endpoint/ End of Stage 1 or 2/ Long-term Follow-up[f]
Blinded Placebo (0 mg)	PI	2 (100.0)/ 1 (25.0)	0/ 0/ 0/ 0/ 0	0/ 0/ 1 (50.0)/ 0/ 0	-	0/ -/ 1 (50.0)
	SI	1 (50.0)/ 0	0/ 0/ 0/ 0/ 0	0/ 0/ 0/ 0/ 0	-	0/ -/ 0
	PB	1 (50.0)/ 0	0/ 0/ 0/ 0/ 0	0/ 0/ 0/ 0/ 0	-	0/ -/ 0
	N	2/ 2	2/ 2/ 2/ 2/ 2	2/ 2/ 2/ 2/ 2	-	2/ -/ 2
Blinded Comparator (25-40 mg)	PI	12 (75.0)/ 5 (14.3)	1 (6.3)/ 1 (6.3)/ 0/ 0/ 0	0/ 0/ 0/ 0/ 0	1 (50.0)/ 0/ 0/ 0/ 0	1 (8.3)/ 0/ 1 (7.7)
	SI	3 (18.8)/ 0	0/ 0/ 0/ 0/ 0	0/ 0/ 0/ 0/ 0	0/ 0/ 0/ 0/ 0	0/ 0/ 0
	PB	5 (31.3)/ 0	0/ 0/ 0/ 0/ 0	0/ 0/ 0/ 0/ 0	0/ 0/ 0/ 0/ 0	0/ 0/ 0
	N	16/ 16	16/ 16/ 15/ 16/ 16	14/ 14/ 14/ 14/ 14	2/ 2/ 2/ 4/ 4	12/ 2/ 13
Blinded Active Doses (75-125 mg)	PI	45 (90.0)/ 35 (31.8)	11 (22.0)/ 4 (8.0)/ 6 (12.0)/ 7 (14.3)/ 10 (20.4)	9 (18.8)/ 9 (18.8)/ 5 (10.4)/ 12 (25.5)/ 8 (17.0)	4 (8.0)/ 6 (12.0)/ 3 (8.0)/ 5 (13.5)/ 5 (13.5)	15 (34.9)/ 11 (28.9)/ 13 (27.7)
	SI	21 (42.0)/ 0	0/ 0/ 0/ 0/ 0	0/ 0/ 0/ 0/ 1 (2.1)	0/ 0/ 0/ 0/ 1 (2.7)	2 (4.7)/ 0/ 1 (2.1)
	PB	15 (30.0)/ 1 (0.9)	0/ 0/ 0/ 0/ 0	0/ 0/ 0/ 0/ 0	0/ 0/ 0/ 0/ 0	0/ 0/ 0
	N	50/ 50	50/ 50/ 50/ 49/ 49	48/ 50/ 48/ 47/ 47	38/ 38/ 38/ 37/ 37	43/ 38/ 47
Open-label Stage 2 Active Dose (100-125 mg)[e]	PI	39 (90.7)/ 22 (51.2)	9 (14.1)/ 3 (4.7)/ 5 (8.8)/ 7 (12.7)/ 6 (10.9)	5 (7.8)/ 2 (3.1)/ 3 (4.9)/ 4 (6.6)/ 4 (6.8)	3 (7.3)/ 1(2.4)/ 1 (1.9)/ 2 (3.8)/ 2 (3.7)	5 (10.9)/ 3 (12.5)[g]/ 0
	SI	21 (48.8)/ 0	0/1 (1.6)/1 (1.6) /2 (3.1)/ 0	0/ 0/ 0/ 0/ 1(1.7)	0/0/0/0/0	0/ 0/ 0
	PB	20 (46.5)/ 0	0/ 0/ 0/ 0/ 0	0/ 0/ 0/ 0/ 0	0/0/0/0/0	0/ 0/ 0
	N	43/ 43	64/ 64/ 57/ 55/ 55	64/ 64/ 61/ 61/ 59	41/ 41/ 54/ 53/ 54	46/ 24/ 6

(1) MPVA-1 data included PTSD participants only, excluded CSOs (concerned significant others) and offered only two Experimental Sessions.
(2) Abbreviations: PI=Positive Ideation, SI=Serious Ideation, PB=Positive Behavior, O=Observations, N=Number of Participants, D1=Day 1, D2=Day 2, D7=Day 7
[a] Lifetime accounts for suicidality prior to study enrollment. [b] Pre-drug Exposure represents measures taken during the Preparatory Session prior to the first Experimental Session. [c] Pre-drug measurement taken on the day of Experimental Session prior to drug administration. [d] During-drug observation measured, on the day of Experimental Session, approximately 6 hours after drug administration.
[f] Post-treatment: 1° or 2° Endpoint excluded MPVA-1; End of Stage 1/ Stage 2 excluded MP16 and MP17; Long-term Follow-up excluded MP16 and MP17.
[g] End of Stage 1/End of Stage 2: For MPVA1, 3-month follow-up used for End of Stage 1/End of Stage 2.

Figure 5: CSSR-S Positive Ideation in MP16 and MP17 (N=37)



		Session 1 (Visit 5)	Session 2 (Visit 10)	Session 3 (Visit 15)
Lifetime	33			
Baseline	19			
Pre-drug		9	4	2
Post-drug		2	2	1
Integrative Day 1		3	3	1
Integrative Day 2		3	3	2
Integrative Day 7		5	4	2

Notes: (i) open-label administration; (ii) positive ideation score > 0

C-SSRS in Social Anxiety in Autistic Adults

In MAA-1, the MDMA study in autistic adults, 0 to 12.5% of participants had a history of serious suicidal ideation and 12.5 to 25.0% reported suicidal behavior. During the preparatory phase prior to blinded drug administration, there were no reports of suicidal ideation or behavior. There was one report of positive ideation on the day of an MDMA-assisted session, and one on the day following. At endpoints, 25.0 to 50.0% had positive ideation. Two participants reported positive ideation, although not serious, during follow-up which may have resulted from ending the therapeutic relationship. These participants were transitioned to non-study therapists and went back on psychiatric medications under the care of their prescribing physician. No serious ideation or behavior occurred during the study. Generally, rates of suicidal thoughts were lower in this population than the PTSD sample (see Appendix Tables 10-12).

C-SSRS in Anxiety Associated with a Life-threatening Illness

In MDA-1, in participants with a life-threatening illness, 0 to 20.0% of participants had a history of serious ideation and 0 to 23.1% reported positive behavior. During the preparatory phase prior to blinded drug administration, one participant experienced positive behavior, and 25.0% had positive ideation. There were no reports of suicidal ideation or behavior during the Preparatory Sessions or during the treatment period. One occurrence of positive ideation was recorded at the Primary Endpoint and long-term follow-up (see Appendix Tables: 13-16).

Summary of Suicidal Ideation and Behavior Across Populations and Indications

Overall the incidence of serious suicidal ideation or behavior in sponsor-supported studies was low, fluctuating in some participants post treatment with MDMA and psychotherapy, and returning to category 1 to 3 suicidal ideation scores while participants were closely monitored. Given that severe PTSD sufferers are known to experience suicidal ideation and behavior, it is difficult to identify a single cause of the increase in suicidal thinking or behavior (i.e., exacerbation of PTSD symptoms, MDMA-stimulated effects, or processing of traumatic memories during psychotherapy with MDMA). A large percentage of people enrolled in the studies reported suicidal ideation and behavior during sometime in their lives prior to study enrollment, which may reflect a manifestation of PTSD or co-morbid affective disorders. When positive serious ideation or behavior occurred after enrollment, the investigators made follow-up observations of C-SSRS to ensure subject safety and tracked scores until they returned to non-serious levels. Frequency of ideation and behavior was greater in the PTSD population compared to healthy individuals, autistic adults, and people with life-threatening illnesses.

Suicidality from Reports of Adverse Events

As of 30 April 2020, three serious adverse events of suicidal ideation were reported across MAPS-supported Phase 2 and Phase 3 studies. Suicidal ideation was reported in a participant in study MP-8, reported 6 days after treatment with 30 mg MDMA and lasted 6 days, concurrent with increased depressive symptoms triggered by external trauma cues, and was treated with prescription medication and hospitalization. The participant who experienced suicidal ideation later experienced depression that was rated serious and unrelated to the Investigational Product, with the event occurring approximately 9 months after a final Experimental Session. The episode resolved approximately 3 weeks after it developed. Depression in this subject was rated severe. The depression led to hospitalization, and the participant reported full recovery after the episode. In an extension to study MP-1 involving a single, additional administration of 125 mg MDMA for participants exhibiting relapse after completing the study, a participant was hospitalized with major depressive episode and suicidal ideation 9 months after the additional Experimental Session, and fully recovered after this episode. In MAPP1, one participant was hospitalized 9 days after the blinded Experimental Session for expressing a worsening feeling of not wanting live and with no plan or intent of self-harm. The participant was prescribed Lexapro by the hospital doctor, released from hospital, and reported feeling better.

As of 30 April 2020, four SAEs of suicidal behavior occurred across MAPS-supported Phase 2 and Phase 3 studies. Two events were reported for one participant in the ongoing, placebo-controlled study MAPP1, and one event in one person in the open-label study MP16, and one in study MP-2. In MP-2, prior to the collection of formal suicidal ideation with C-SSRS, one participant was hospitalized for suicidal behavior that allegedly developed after a conflict with her ex-husband 2 weeks prior to drug administration, indicating that suicidal ideation and behavior can occur at baseline prior to drug administration. This subject fully recovered and went on to participate in the study. In the case occurring in MP16, the therapists learned of a recent suicide attempt during an Integrative Session, possibly arising from apprehension about the study ending. The

participant was admitted to the ER overnight, and fully recovered in the subsequent day. In the first of the two events in the participant in the ongoing, placebo-controlled MAPP1 study, the participant ingested a combination of over the counter medications, and acknowledged suicidal ideation, but followed instructions not to consume alcohol. This was considered an occurrence of testing the therapists, but after discussion was coded as a suicide attempt. The second event occurred 2 months later, still within the blinded portion of the MAPP1 study.

6.4.3 Vital Signs

In all sponsor-supported studies to date, vital signs readings (temperature, blood pressure, and heart rate) were taken at baseline, with study-specific differences in data collection times post-drug. The data presented in the below sections is final for completed studies and preliminary for studies ongoing at the time of the data cutoff.

6.4.3.1 Body Temperature

In most sponsor-supported studies to date, tympanic body temperature readings were taken at baseline, then every 60 to 90 minutes after drug administration during each blinded or open-label Experimental Session, with some differences in collection methods across studies. Peak values during each Experimental Session were ascertained for all studies. Across studies, the final value was either at a relatively set time (MP-8, MP-12, MP1-E2, MP16, MP17, MPVA-1) or as the final reading with varying time points (MP-1). In the MP-1 and MP-2 studies two pre-drug values were reported (15 minutes and 5 minutes before dosing) and the results of these measurements were averaged. Average post-drug values served as the final value for MP-2. If body temperature rose >1°C above the pre-drug (baseline) reading, each duration above specific values required more frequent monitoring as listed in the study protocols. Clinical signs and symptoms were monitored and more frequent readings of body temperature were collected in cases where readings were above these values.

Table 15: Pre-Drug, Peak, and Final Body Temperature (ºC) During Experimental Sessions with Placebo or any MDMA Dose in MAPS-Sponsored Studies of PTSD (MP-1, MP-2, MP-4, MP-8, MP-12)

Dose	N	Pre-drug Mean (SD) Min/Max	Peak Mean (SD) Min/Max	Final Mean (SD) Min/Max	N (%) with BT 1 ° C above Baseline
Placebo	10	36.4 (0.51) 35.1/37.2	36.9 (0.36) 36.4/37.6	36.6 (0.36) 35.9/37.5	2 (20.0)
25 mg	8	36.4 (0.39) 35.5/37.1	37.2 (0.78) 36.0/38.5	36.8 (0.65) 35.4/38.0	4 (50.0)
30 mg	7	36.2 (0.47) 35.3/36.9	37.0 (0.42) 36.4/37.9	36.6 (0.47) 35.7/37.3	4 (57.1)
40 mg	6	36.4 (0.50) 35.8/37.2	37.1 (0.33) 36.6/37.6	37.0 (0.38) 36.5/37.6	2 (33.3)
75 mg	7	36.6 (0.46) 35.9/37.8	37.1 (0.52) 36.3/37.8	36.7 (0.42) 36.1/37.3	2 (28.6)
100 mg	9	35.9 (1.00) 33.9/37.9	37.0 (0.64) 35.5/38.7	36.5 (0.74) 34.8/38.1	4 (44.4)

125 mg	58	36.5 (0.47) 35.4/37.6	37.3 (0.49) 36.1/38.6	36.9 (0.54) 34.5/38.2	26 (44.8)
Open-label (100-150 mg)	78	36.4 (0.54) 34.3/37.7	37.3 (0.57) 36.0/38.7	36.8 (0.58) 35.2/38.4	39 (50.0)

In MAPS-sponsored PTSD studies MP-1 to MP-12, body temperature above (1°C above pre-drug reading) was detected in 44% (42 of 95) participants who received any dose of MDMA during blinded sessions and 50% (39 of 78) participants receiving 100 to 150 mg MDMA during open-label sessions. Note that body temperature above 1°C above pre-drug reading was observed in 20% (2 of 10) of participants who received placebo. End of session temperature readings were lower than peak drug readings, though they remained above pre-drug measurements. Body temperature increases that were 1°C or more above initial temperature occurred in all dose groups, suggesting a minimal role for dose. The maximum body temperature observed for any subject receiving MDMA was 38.7°C, observed after a 100 mg MDMA blinded session, and during open-label sessions. No participants required medical intervention to decrease body temperature and values returned to baseline as drug effects waned. Body temperature measured during Experimental Sessions in sponsor-supported studies of PTSD was commensurate with values seen in Phase 1 clinical trials described above.

In the MAPS study MAA-1, body temperature 1°C above pre-drug reading was detected in 28.6% (2 of 7) participants who received 100 mg of MDMA during a blinded session. Body temperature above the 1°C increase predetermined as cause for increased assessment did not occur during open-label sessions with 75 or 125 mg MDMA. The maximum body temperature observed for any subject receiving MDMA in MAA-1 was 37.7°C. No participants required medical intervention to decrease body temperature and values dropped below peak values or returned to baseline as drug effects waned. Body temperature measurements in this sample were similar to those reported in Phase 1 studies and the sample of people with PTSD (see Appendix Tables 2, 4, 6, and 8 for data).

In the MAPS study-Phase 2 clinical trial of MDMA-assisted psychotherapy for anxiety in relation to a life-threatening illness (MDA-1), body temperature rose 1°C above pre-drug reading in 53.8% (7 of 13) of participants receiving MDMA during blinded Experimental Sessions and in none of the participants given placebo during blinded sessions. Body temperature rose 1°C above pre-drug reading in 52.9% (9 of 17) participants during open-label sessions. Body temperature recorded at end of session was lower than peak body temperature. The maximum body temperature observed for any subject receiving 125 mg MDMA was 39.9°C. No participants required medical intervention to decrease body temperature and values returned to baseline as drug effects waned (see Appendix Tables 3, 5, 7, and 9 for data).

In MPVA-1, vital signs were assessed on the day of MDMA-assisted sessions prior to drug dosing, just before the optional supplemental dose (midpoint), and at the end of the session. The maximum body temperature observed for any subject receiving 75 or 100 mg MDMA was 38.4°C and the mean (SD) temperature prior to the supplemental dose was 37.1°C (SD=0.53) in the CSO participant and 37.2°C (SD=0.48) in the PTSD+ participant.

Based on the literature, MDMA is expected to produce elevations in body temperature with possible influence of ambient temperature. In the above MAPS-sponsored studies, adjustments were made to the ambient temperature and to air circulation in the room in response to observed elevation in body temperatures, but no participants required medical intervention to decrease body temperature, and values returned to baseline as drug effects waned. In conclusion, controlled settings for treatments with MDMA-assisted psychotherapy were optimized with the capacity to control the ambient temperature for subject comfort, though there is no evidence that these measures significantly influenced or were needed for control of core body temperature.

6.4.3.2 Cardiovascular System

In all sponsor-supported studies to date, blood pressure readings were taken at baseline, with study-specific differences in data collection times after drug administration. Peak values during each Experimental Session were ascertained for studies MP1 through MP12 (Appendix Table 15). In MP16, MP17, and MPVA-1, peak values were collected just prior to the optional supplemental dose (midpoint). The final or endpoint was recorded as the final value at a relatively set time (MP-8, MP-12, MP16, MP17, MPVA-1), as the final value available, or with varying timepoints (MP-1). MP-1 and MP-2 reported two pre-drug values (15 minutes and 5 minutes before dosing) and the results of these measurements were averaged, whereas all other studies reported a single time point pre-drug. Average post-drug values served as the final value for MP-2. If systolic blood pressure (SBP) rose above 160 mmHg or if diastolic blood pressure (DBP) rose above 110 mmHg, additional measurements were collected in studies MP-8, MP-12, MP-9, and MP-4. In MAA-1, if SBP rose above 180 mmHg or if DBP rose above 110 mmHg, each duration above the pre-determined cut-off was collected. If SBP rose above 180 mmHg and DBP rose above 120 mmHg, each timepoint above the pre-determined cut-off was collected in MDA-1. The cut-off for blood pressure (as SBP/DBP) in MP-2 was >160/110 mmHg. Clinical signs and symptoms were monitored and more frequent readings were collected in cases where readings were above the cut-off. Systolic and diastolic pressure data are presented separately. SBP results are summarized in Table 16 and DBP results summarized in Table 18, and in Appendix Tables 4-7. Values recorded during blinded sessions and those from open-label sessions are reported separately (see Table 16, 18 and Appendix Tables 4-7).

Candidates with hypertension were excluded from participation in early sponsor-supported studies, but more recent studies have allowed enrollment of participants with well-controlled hypertension. For example, in MP-8, four participants with hypertension controlled by medications were permitted to enroll after completion of carotid ultrasound and nuclear stress test (per protocol) in addition to usual medical screening for the study (see Table 17 and Table 19, below, for data from these participants).

Systolic Blood Pressure

The observed increase in SBP was greater when doses of 75 mg or more of MDMA were administered. In MAPS-sponsored PTSD studies MP-1 through MP-12, systolic blood pressure above 160 mmHg was detected in 32% (30 of 95) participants who received

MDMA at any dose during blinded sessions. It is notable that the majority of these cases occurred after 125 mg of MDMA but failed to occur after inactive placebo or doses lower than 30 mg. SBP rose above 160 mm Hg in 36% (28 of 78) participants after 100 to 150 mg of MDMA in open-label sessions. Similar to blinded sessions, SBP returned to baseline levels at the end of the session. The maximum systolic blood pressure for any subject receiving MDMA was 200 mmHg. Final (end of session) values returned to pre-drug levels with no clinical intervention required. No clinically significant AEs were reported based on elevations in blood pressure and no treatment was required for these transient elevations of blood pressure.

In, the MPVA-1 study, after two open-label sessions with 75 to 100 mg MDMA, both members of dyads consisting of people with PTSD and concerned significant others exhibited a rise in systolic blood pressure in a study of MDMA-assisted psychotherapy and cognitive-behavioral conjoint therapy (CBCT). SBP returned to near baseline levels at the closing of an Experimental Session, with final readings 0.5 to 2.6 units higher than baseline. Additional or high SBP values were not recorded for any of the participants. Peak SBP was not recorded per protocol. Observed SBP did not appear to differ on the basis of PTSD diagnosis. Maximum recorded SBP during this study was 180 mmHg in a concerned significant other at Experimental Session midpoint.

Table 16: Pre-drug, Peak, and Final Systolic Blood Pressure During Experimental Sessions with Placebo or any MDMA Dose in MAPS-Sponsored Studies of PTSD (MP-1, MP-2, MP-4, MP-8, MP-12)

Dose	N	Pre-drug Mean (SD) Min/Max	Peak Mean (SD) Min/Max	Final Mean (SD) Min/Max	N (%) with SBP Above 160 mm Hg
Placebo	10	114.9 (11.61) 90.5/136.5	129.7 (15.27) 102.0/157.0	111.4 (12.88) 83.0/133.0	0
25 mg	8	119.3 (7.13) 107.0/141.0	132.5 (9.09) 114.0/147.0	119.3 (11.23) 107.0/146.0	0
30 mg	7	114.0 (11.91) 94.0/134.0	132.3 (14.02) 110.0/155.0	118.5 (11.63) 98.0/140.0	0
40 mg	6	124.7 (14.14) 100.0/154.0	134.3 (15.47) 112.0/163.0	123.6 (12.52) 107.0/148.0	1 (16.7)
75 mg	7	125.4 (9.99) 109.0/145.0	147.0 (14.43) 123.0/179.0	127.4 (11.85) 107.0/147.0	1 (14.3)
100 mg	9	121.4 (20.16) 96.0/161.0	138.6 (23.55) 100.0/180.0	116.7 (13.50) 92.0/140.0	2 (22.2)
125 mg	58	126.2 (16.03) 98.0/177.0	153.7 (18.49) 114.0/200.0	127.3 (16.25) 86.0/168.0	26 (44.8)
Open-label 100-150 mg	78	124.1 (14.37) 95.0/171.0	151.1 (17.10) 105.0/193.0	124.7 (14.88) 77.0/161.0	28 (35.9)

In MP-8, systolic blood pressure above 160 mmHg was detected in 75% (3 of 4) of participants with hypertension kept controlled by medication during blinded sessions with 30 to 125 mg MDMA and in 67% (2 of 3) participants receiving 100 to 125 mg MDMA during open-label sessions. No increase in SBP >160 mmHg occurred after administration of 30 mg MDMA. The maximum systolic blood pressure for these participants with controlled hypertension was 193 mmHg, which occurred during an open-label session. The baseline values and elevations after MDMA appear higher in this sub-group than the overall sample but any meaningful comparison is limited by the

sample size. Pre-drug SBP was typically higher in this sub-group, and peak SBP of these participants was typically at the upper end of the range of the overall sample. Final SBP readings remained 11 to 14 mmHg higher on average than pre-drug SBP readings in the subject who received 75 mg of MDMA in two blinded Experimental Sessions and 100 mg in three open-label crossover Experimental Sessions. However, two participants who received 125 mg MDMA had final readings that returned to pre-drug values, which might suggest these could have been due to these individual's medical history of both hypertension and hyperlipidemia. One subject with controlled hypertension dropped out (not due to blood pressure concerns) after receiving a single Experimental Session with 30 mg MDMA but did not experience SBP above 160 mmHg. None of the participants with controlled hypertension experienced AEs of the cardiovascular system and SBP returned to baseline or near-baseline levels at final session reading without any additional medication.

Table 17: Pre-drug, Peak, and Final Systolic Blood Pressure During Experimental Sessions in Controlled Hypertension Participants in MAPS-Sponsored PTSD Study MP-8

Dose	N	Pre-drug Mean (SD) Min/Max	Peak Mean (SD) Min/Max	Final Mean (SD) Min/Max	SBP Above 160 mm HG N
30 mg	1	125 125/125	131 131/131	124 124/124	0
75 mg	1	139 (8.49) 133/145	174.5 (6.36) 170/179	147 147/147	1
125 mg	2	130.8 (11.53) 124/148	160.5 (13.30) 147/177	128.5 (9.54) 118/141	2
Open-label 100-125 mg	3	139.2 (18.97) 122/171	174.6 (18.47) 144/193	142.8 (10.28) 133/158	2

In the MAA-1 study, systolic blood pressure did not rise above 180 mmHg during blinded sessions with inactive placebo or 75 to 125 mg MDMA, nor during open-label sessions with 75 to 125 mg MDMA [536]. The maximum systolic blood pressure for any subject receiving MDMA was 174 mmHg, which occurred after 75 mg MDMA. Peak SBP values in this sample suggests slightly lower values than in studies in people with PTSD, but the sample was much smaller, and this may reflect a chance fluctuation. It is also notable that, in general, this study employed lower active doses of MDMA than the PTSD studies. Final values returned to pre-drug levels with no clinical intervention required. No clinically significant AEs were reported based on elevations in blood pressure (see Appendix Table 4).

In the MDA-1 study, systolic blood pressure rose above threshold (180 mmHg) in 54% (7 of 13) of participants who received 125 mg MDMA during blinded sessions and in 29% (5 of 17) after open-label 125 mg sessions. In comparison, SBP above 180 mm Hg was detected in 40% (2 of 5) of participants who received placebo. The maximum systolic blood pressure for any subject receiving MDMA was 196 mmHg, observed after 125 mg in an open-label session. Final values returned to pre-drug levels with no clinical intervention required. No clinically significant AEs were reported based on elevations in blood pressure. SBP values in this sample appear to be similar to values reported in sample with PTSD (see Appendix Table 5).

In all cases across studies, final values returned to pre-drug levels with no clinical intervention required. No clinically significant AEs were reported based on elevations in blood pressure.

Diastolic Blood Pressure

In MAPS-sponsored PTSD studies, doses of 75 and 125 mg MDMA produced greater elevation in DBP than lower doses of 25 to 40 mg. The lower increase in DBP after 100 mg MDMA may reflect random variation in a small sample. At the end of session or final reading, DBP had returned to baseline levels across all doses of MDMA. DBP above 110 mmHg was detected in 7% (7 of 95) of participants who received any dose of MDMA during blinded study sessions, and 6.4% (5 of 78) participants who received 100 to 150 mg MDMA during open-label sessions. The maximum diastolic blood pressure for any subject receiving MDMA was 135 mmHg, and no clinical intervention was required. No clinically significant AEs were reported based on elevations in blood pressure. These observations suggest that people with PTSD experience similar elevations in SBP and DBP as those seen in healthy controls.

MPVA-1 was the open-label study of MDMA-assisted psychotherapy and CBCT in dyads made up of one person with PTSD and a significant other without PTSD. DBP was elevated at midpoint compared with baseline in both groups (3.6 to 11.3 mmHg) and returned to near-baseline levels after 75 to 100 mg MDMA. DBP returned to baseline or near-baseline levels at session end (dropping 4.5 to 7.5 mmHg). The highest value was recorded at midpoint (106 mm Hg). No additional readings were required during either Experimental Session.

Table 18: Pre-drug, Peak, and Final Diastolic Blood Pressure During Experimental Sessions with Placebo or any MDMA Dose in MAPS-Sponsored Studies of PTSD (MP-1, MP-2, MP-4, MP-8, MP-9, MP-12)

Dose	N	Pre-drug Mean (SD) Min/Max	Peak Mean (SD) Min/Max	Final Mean (SD) Min/Max	N (%) with DBP Above 110 mm Hg
Placebo	10	72.7 (7.88) 56.5/87.5	83.4 (9.73) 65.0/102.0	68.5 (9.71) 48.0/89.0	0
25 mg	8	73.4 (6.44) 59.0/84.0	82.7 (5.30) 74.0/92.0	71.9 (5.43) 63.0/81.0	0
30 mg	7	73.5 (8.03) 60.0/87.0	85.5 (7.52) 75.0/99.0	76.7 (6.23) 68.0/91.0	0
40 mg	6	80.0 (9.96) 62.0/95.0	86.1 (9.28) 72.0/96.0	79.9 (9.74) 68.0/96.0	0
75 mg	7	77.9 (9.73) 56.0/95.0	91.4 (12.06) 78.0/118.0	78.4 (11.19) 59.0/100.0	1 (14.3)
100 mg	9	79.0 (13.45) 58.0/102.0	84.4 (11.38) 65.0/101.0	74.4 (7.72) 61.0/88.0	0
125 mg	58	79.5 (10.03) 52.0/102.0	92.5 (10.88) 70.0/135.0	78.6 (10.27) 53.0/104.0	6 (10.3)
Open-label 100-150 mg	78	78.1 (9.31) 56.0/103.0	92.8 (10.8) 64.0/126.0	77.5 (9.79) 54.0/100.0	5 (6.4)

In MP-8, participants with controlled hypertension responded similarly to MDMA as normotensive people, with final values returning to at- or near-baseline levels, and peak levels higher after 75 to 125 mg MDMA compared with 30 mg MDMA. Diastolic blood pressure above 110 mmHg was detected in 25% (1 of 4) participants with controlled hypertension in blinded sessions and in one of three participants who received 100 to 125 mg MDMA during open-label sessions. The maximum DBP for these participants with controlled hypertension was 125 mmHg. Final values returned to pre-drug levels at end of session with no clinical intervention required. No clinically significant AEs were reported based on elevations in blood pressure.

Table 19: Pre-drug, Peak, and Final Diastolic Blood Pressure During Experimental Sessions in Controlled Hypertension Participants in MAPS-Sponsored PTSD Study MP-8

Dose	N (Observations)	Pre-drug Mean (SD) Min/Max	Peak Mean (SD) Min/Max	Final Mean (SD) Min/Max	DBP Above 110 mm Hg N (Observations)
30 mg	1	85 85/85	86 86/86	77 77/77	0
75 mg	1 (2)	92 (4.24) 89/95	115.5 (3.54) 113/118	95.5 (6.36) 91/100	1 (2)
125 mg	2 (4)	86.0 (6.68) 79/95	97.0 (6.06) 91/105	83.0 (7.62) 72/89	0
Open-label 100-125 mg	3 (5)	86.8 (9.39) 77/101	114.4 (13.3) 93/125	91.2 (6.10) 82/99	1 (3)

In the MAA-1 study, MDMA produced greater elevation in DBP than inactive placebo: an increase of 5.4 mmHg after placebo versus an increase of 11.8 mmHg after 75 mg, 15.4 mmHg after 100 mg, and 10.5 mmHg after 125 mg, respectively. At the end of the session, DBP returned to baseline levels in all blinded and open-label Experimental Sessions. DBP above 110 mmHg was not detected during any session, regardless of dose. The maximum DBP for any subject receiving MDMA was 106 mmHg, which occurred after inactive placebo administration. Final (end of session) values returned to pre-drug levels with no clinical intervention required. No clinically significant AEs were reported based on elevations in blood pressure (see Appendix Table 6).

In the MDA-1 study, peak DBP was higher after 125 mg MDMA than after inactive placebo as expected, and final values returned to pre-drug levels with no clinical intervention required. Diastolic blood pressure above 120 mmHg was detected in 31% (4 of 13) participants who received 125 mg MDMA during blinded sessions and 11.8% (2 of 17) participants receiving MDMA during open-label sessions. In comparison, diastolic blood pressure above threshold was detected in 20% (1 of 5) of participants who received placebo. The maximum DBP for any subject receiving MDMA was 154 mmHg, which was observed in a subject who received 125 mg MDMA. No clinically significant AEs were reported based on elevations in blood pressure and DBP returned back to pre-drug levels with no treatment required (see Appendix Table 7).

Summary of SDB/ DBP

MDMA was expected to produce transient, increases in blood pressure that returned to baseline or near-baseline values. The supplemental half dose, when administered 1.5 to 2.5 hours after the initial dose, may cause further SBP increases above that of the initial dose of MDMA. In one study (MP-1), 9 of 23 participants received the supplemental dose, with four in the 125 mg MDMA group. In all subsequent studies, most of the participants received the optional supplemental dose. A comparison of participants receiving the supplemental dose to those who only received the initial dose in MP-1 indicated that the supplemental dose did not cause further elevation in blood pressure or heart rate beyond the initial dose, although the sample was underpowered to detect a significant effect. Maximum SBP observed to date was 200 mmHg in a single MP-2 subject who was administered 125 mg MDMA as the initial dose which lasted 5 hours. This subject had a medical history of controlled hypertension, and the traumatic event that caused PTSD was medical malpractice, with a secondary diagnosis of white coat hypertension. This subject was only enrolled after 24-hour monitoring of blood pressure at baseline to confirm this diagnosis. Despite elevations in SBP, no clinical signs or symptoms of hypertension were observed and no additional treatment was required. In all cases across the Clinical Development Program, including in participants with PTSD, autistic adults with social anxiety, and people with anxiety arising from facing a life-threatening illness, blood pressure returned to pre-drug levels at end of session with no clinical intervention required. No clinically significant AEs were reported based on elevations in blood pressure.

Heart Rate

In all sponsor-supported studies to date, heart rate readings were taken at baseline, with study-specific differences in data collection times after drug administration. Peak values during each Experimental Session were ascertained for all studies. The final or endpoint value was recorded as the final value, either at a relatively set time (MP-4, MP-8, MP-9, MP-12, MP16, MP17, MPVA-1) or as the final value available, with varying time points (MP-1). MP-1 and MP-2 reported two pre-drug values (15 minutes and 5 minutes before dosing) and these measurements were averaged, whereas all other studies reported single time point pre-drug value. Average post-drug values serve as the final value for MP-2. If heart rate rose above 110 beats per minute (bpm), each duration above the pre-determined cut-off was collected in MP-8, MP-12, MP-9, and MP-4. Duration of pulse above cut-off was not collected in MP-2. Clinical signs and symptoms were monitored, and more frequent readings were collected in cases where readings were above the pre-determined cut-off.

Table 20: Pre-drug, Peak, and Final Heart Rate During Experimental Sessions with Placebo or any MDMA Dose in MAPS-Sponsored Studies of PTSD (MP-1, MP-2, MP-4, MP-8, MP-9, MP-12)

Dose	N	Pre-drug Mean (SD) Min/Max	Peak Mean (SD) Min/Max	Final Mean (SD) Min/Max	N (%) with HR Above 110 BPM
Placebo	10	64.9 (11.53) 45.0/91.0	77.8 (13.02) 54.0/107.0	67.6 (11.14) 45.0/89.0	0
25 mg	8	69.6 (13.14) 47.0/94.0	84.2 (19.27) 50.0/124.0	72.4 (12.37) 51.0/90.0	2 (25.0)
30 mg	7	67.7 (13.89) 45.0/91.0	81.1 (15.98) 54.0/102.0	72.7 (13.01) 50.0/89.0	0
40 mg	6	79.1 (11.00) 66.0/103.0	87.5 (11.51) 69.0/103.0	80.1 (15.50) 56.0/103.0	0
75 mg	7	73.7 (8.31) 61.0/85.0	96.2 (16.12) 75.0/123.0	82.9 (13.34) 63.0/102.0	2 (28.6)
100 mg	9	70.8 (17.40) 46.0/118.0	97.0 (21.50) 65.0/140.0	81.4 (13.21) 63.0/114.0	3 (33.3)
125 mg	58	74.8 (13.89) 45.0/122.0	103.2 (16.75) 67.0/160.0	85.6 (15.56) 47.0/135.0	29 (50.0)
Open-label 100-150 mg	78	74.0 (14.98) 36.0/116.0	106.0 (20.28) 63.0/156.0	83.7 (14.72) 52.0/120.0	36 (46.2)

In MAPS-sponsored PTSD studies, MDMA appears to increase peak heart rate compared with placebo, with a greater difference between pre-drug and peak values observed with active doses, and greater differences between peak and pre-drug for every dose except for 40 mg during blinded sessions. In PTSD studies, heart rate was temporarily elevated above 110 bpm was detected in 38% (36 of 95) of participants receiving MDMA in blinded Experimental Sessions, and heart rate never arose above threshold in placebo subjects. Heart rate was elevated above 110 BPM in 46% (36 of 78) of participants given 100 to 150 mg MDMA in open-label sessions. The maximum heart rate for any subject receiving MDMA was 160 bpm. Values at end of session returned to pre-drug levels with no clinical intervention required. No clinically significant AEs were reported based on elevations in heart rate.

In the MPVA-1 open-label study of CBCT combined with MDMA-assisted psychotherapy in dyads, which comprised of a person diagnosed with PTSD and a significant other without PTSD, heart rate was recorded at baseline, midpoint, and at Experimental Session end. Heart rate was elevated by 15.8 to 19.6 BPM at session midpoint, prior to administering supplemental dose of MDMA, compared with baseline in participants with and without PTSD respectively. Mid-session HR was elevated compared with baseline in participants with and without PTSD. Heart rate remained above baseline at the end of the session. The highest value was 137 BPM, recorded at session midpoint in a PTSD participant. No extra readings were taken for any participant. No cardiac disorder AE was reported.

In the MAA-1 study, peak heart rate increased ranging from 15 bpm after inactive placebo to 16.5 bpm after 125 mg MDMA in blinded sessions, and from 13 to 23 bpm after open-label sessions. In most cases, heart rate had returned to baseline levels or near baseline levels, except after blinded 125 mg, where average final reading remained 15.7 bpm greater than baseline. However, this dose group consisted of only three individuals. Heart rate above 110 bpm was detected in 14% (1 of 4) of participants given MDMA during blinded Experimental Sessions and in none of the participants receiving placebo

during blinded Experimental Sessions or after open-label sessions with 75 to 125 mg MDMA. The maximum heart rate for any subject receiving MDMA was 114 bpm. No clinical intervention was required during the study. No clinically significant AEs were reported based on elevations in heart rate (see Appendix Table 8).

In MAPS-sponsored MDA-1, MDMA produced a greater increase in heart rate than inactive placebo during blinded and open-label sessions. End of session heart rate was lower than peak value for all dose groups, with end of session heart rate at pre-drug levels after placebo and lower than peak value but at least 15.5 bpm higher than pre-drug levels after 125 mg MDMA in blinded or open-label sessions. Elevation in heart rate above threshold 120 bpm) was detected in 46% (6 of 13) of participants given 125 mg MDMA during blinded Experimental Sessions and in none of the participants who received inactive placebo. Heart rate elevation above cut off was seen in 35.3% (6 of 17) of participants given 125 mg MDMA during open-label Experimental Sessions. This study was comprised of a small sample, making comparisons with other samples or with healthy controls difficult. The maximum heart rate for any subject receiving MDMA was 140 bpm, observed after 125 mg MDMA during an open-label session. No clinical interventions were required, and no clinically significant AEs were reported based on elevations in heart rate (see Appendix Table 9).

Summary of Cardiovascular Effects

The values presented above suggest a dose-dependent transient increase in SBP and heart rate, which is supported in the literature in studies with healthy volunteers [17, 19, 20, 538]. While peak DBP was higher after MDMA doses of 100 mg or greater, very few reports of DBP elevated above cut-off occurred during MDMA administration, which suggests that this was a less common response than elevated SBP or pulse.

On average, cardiovascular vital signs returned to baseline or near-baseline values by final reading, which is the case across all doses of MDMA. Blood pressure and pulse readings permitted the detection of the SAR of increased ventricular extrasystoles described in Section 6.4.1.4 Serious Adverse Reactions, but elevated blood pressure or pulse were not the cause of the event. There were far fewer observations of above threshold values of DBP than SBP. None of the participants have required medical intervention after elevations above cut-off, and the elevations were self-limiting, and none were clinically significant.

6.4.4 Hepatic System and Other Laboratory Values

The first two sponsor-supported Phase 2 studies (MP-1, MP-2) assessed liver function after completion of two or three blinded Experimental Sessions. Values that differ from established age-appropriate norms were evaluated for clinical significance. Laboratory assessments of liver function were not conducted after Experimental Sessions in subsequent sponsor-supported studies and no AEs related to liver function have been reported in these studies.

Table 21: List of All Clinically Significant Changes in Laboratory Values in Two Participants from MP-2

Laboratory Value	Abnormal Test Value	Value at Baseline	Normal Value/Range	Dose
Bilirubin	2.8	2.2	<2.5 mg/dL	125 mg
ESR	32	2.4	<10 mm	125 mg

[1] Post-drug liver panels or other laboratory tests were not conducted in studies subsequent to studies MP-1 and MP-2.

One participant in the MP-2 study reported a clinically significant hepatic result, which re was an elevation in bilirubin that occurred after open-label treatment with 125 mg to 150 mg initial dose of MDMA. The participant had reported a family history of elevated bilirubin. Family history of mildly elevated bilirubin is considered an indicator of Gilbert's syndrome which is a benign liver condition where the liver does not properly process bilirubin. Liver enzymes were normal at the same time when the elevated bilirubin was reported.

Table 22: Average ALT Values at Baseline and 2-Month Follow-up After Two Experimental Sessions in Participants from MP-1

Timepoint	Placebo	125 mg
Baseline	25.6 (13.4) N=8	22.75 (12.89) N=12 [a]
Primary Endpoint After Two Experimental Sessions	26.4 (13.5) N=8	19.7 (12.7) N=13

[1] Subsequent studies did not measure post-drug liver panels or other laboratory tests.
[a] ALT value for one subject not recorded at baseline.

No clinically significant changes in liver function occurred in MP-1. All values for hepatological laboratory tests were within the normal range in MP-1.

Other Abnormal Laboratory Results

Another participant in the MP-2 study reported a clinically significant abnormality. A laboratory finding of elevated erythrocyte sedimentation rate (ESR), a marker of inflammation occurred in a subject with a medical history of breast cancer. This value was recorded 3 months after the last administration of MDMA as an AE unrelated to MDMA.

6.4.5 Cognition and Performance

Acute effects on cognitive function were not assessed in sponsor-supported studies. In three MAPS-sponsored studies, MP-1, MP-4, and MP-12, long-term effects on cognitive function was assessed by administering the Repeatable Battery for Assessment of Neuropsychological Status (RBANS), a relatively brief measure that assesses memory, attention and processing speed, visual-spatial and constructional abilities, and expressive language [658]; and the Paced Auditory Serial Addition Task (PASAT), a measure of auditory processing speed and mental flexibility [659, 660]. These instruments were given prior to and 1 to 2 months after psychotherapy assisted with either full dose MDMA or a comparator/placebo dose.

In MP-1, no significant differences in cognitive function were detected at the 2-month Follow-up between subjects who received two sessions with 125 mg of MDMA compared to participants who received placebo, as measured by RBANS and PASAT [3].

These findings suggest that MDMA did not impair cognitive function in this sample or that the effect was too small to attain statistical significance in this small pilot study. Two completed studies (MP-12 and MP-4) included these measures to assess reproducibility of this finding. Available data pooled across studies are presented by dose in Table 23 and Table 24.

Table 23: Neurocognitive Function - RBANS Mean Total Scores at Baseline, Primary Endpoint, End of Stage 1, and End of Stage 2 for MP-1, MP-4, and MP-12

Dose	Baseline Mean (SD)	Primary Endpoint Mean (SD)	End of Stage 1 Mean (SD)	End of Stage 2 Mean (SD)
Placebo	100.9 (15.38) N=10	106.9 (15.15) N=10	---	117.0 (2.83) N=2
40 mg	94.7 (5.20) N=6	104.0 (9.52) N=4	---	103.3 (5.91) N=4
100 mg	95.9 (15.47) N=8	103.4 (13.98) N=9	99.9 (16.50) N=9	---
125 mg	103.2 (15.11) N=30	103.4 (13.21) N=27	99.9 (12.86) N=14	---

On average, RBANS scores trended towards improvement after treatment with placebo and 40 mg to 100 mg initial dose of MDMA, whereas scores stayed the same after treatment with 125 mg initial dose of MDMA. The trend towards improvement could be a practice effect from repeated assessments, although stimuli were varied across these assessments, or could possibly be correlated with PTSD symptom reduction. One to three additional treatments with open-label active dose MDMA do not appear to worsen cognitive function based on preliminary End of Stage 1 and End of Stage 2 results. The statistical significance of these pooled findings is yet to be determined.

Table 24: Neurocognitive Function - PASAT Trial 1 and Trial 2 Mean Raw Total Scores at Baseline, Primary Endpoint, End of Stage 1, and End of Stage 2 for MP-1, MP-4, and MP-12

		PASAT Trial 1		
Dose	**Baseline Mean (SD)**	**Primary Endpoint Mean (SD)**	**End of Stage 1 Mean (SD)**	**End of Stage 2 Mean (SD)**
Placebo	42.1 (12.59) N=10	43.7 (12.03) N=10	---	40.0 (4.24) N=2
40 mg	44.3 (9.44) N=6	54.3 (3.86) N=4	---	54.5 (5.51) N=4
100 mg	46.5 (11.56) N=8	48.6 (9.32) N=9	50.2 (9.02) N=9	---
125 mg	45.0 (10.92) N=30	49.4 (8.02) N=27	48.9 (9.21) N=14	---
		PASAT Trial 2		
Placebo	34.2 (11.21) N=10	38.6 (11.66) N=10	---	42.5 (3.54) N=2
40 mg	34.8 (12.12) N=6	44.8 (9.18) N=4	---	45.3 (6.70) N=4
100 mg	33.9 (12.25) N=8	33.1 (14.16) N=9	37.8 (12.33) N=9	---
125 mg	33.3 (9.55) N=30	35.8 (8.33) N=26	36.9 (11.12) N=14	---

On average, PASAT scores stayed about the same after treatment with placebo and 100 mg initial dose of MDMA and trended towards improvement after treatment with 40 and 125 mg initial dose of MDMA. The trend towards improvement could be a practice effect from repeated assessments or could be correlated with PTSD symptom reduction. One to three additional treatments with open-label active dose MDMA do not appear to have worsened cognitive function and continued to trend towards improvement on average based on preliminary End of Stage 1 and End of Stage 2 results. Cognitive function tests such as the PASAT are also known to be subject to individual variability, as they require basic proficiency with mathematical skills that are influenced by education level. The significance of these pooled findings has yet to be determined, but it does not appear that MDMA-assisted psychotherapy negatively impacted cognitive function.

6.4.6 Abuse Potential

Subjective Effects

MDMA produces anxiolytic and prosocial effects, which could counteract avoidance and hyperarousal. These subjective effects of MDMA are hypothesized to create a desirable psychological state that enhances the therapeutic process in treating PTSD and other anxiety disorders. Findings using both subjective and objective indices of mood alterations suggest that MDMA generates prosocial feelings and mental states in humans in controlled laboratory settings. These effects may also be associated with determining the abuse liability of MDMA. Subjective effects of moderate doses of MDMA in controlled laboratory settings to healthy non-dependent volunteers, with a range of Ecstasy use history, have been reported in 28 publications summarized in a NIDA-funded review (N=657) [661]. These self-reported ratings include a broad range of mood states with relevance to social behavior.

As presented in Table 25, participants endorsed the following verbatim terms as VAS items: feeling loving, talkative, extroverted, sociable, self-confident, friendly, playful, open, trusting, close to other people, and emotionally concerned. MDMA's subjective prosocial effects may be enhanced in group settings when other individuals have also been administered MDMA in laboratory studies. Increased feelings of loneliness may have resulted from testing conditions where participants receive MDMA in comparative isolation; however, these effects are not dependent on a permissive environment. From latent speech analysis and self-report data, "want more drug" ratings were predictive of prosocial effects, supporting this as the basis for moderate abuse liability of MDMA in healthy volunteers [661, 662].

A prospective pooled analysis of eight controlled non-sponsor supported clinical studies, was conducted in an overall sample of 139 healthy nondependent individuals (mean age 24.9, SD:4.1). In participants receiving 75 mg (N=29) or 125 mg MDMA (N=110), subjective "any drug effect" ratings were significantly higher than regular metabolizers ($p<0.05$) at 0.6 hours post-drug in poor metabolizers with CYP2D6 polymorphisms, which leads to 15% elevated C_{max} of MDMA and 50% elevated C_{max} of MDA. However, these effects were no longer significant at 1.5 hours post-drug.

Table 25: Summary of Ecstasy Use History and Subjective Effects of MDMA Among Healthy Volunteers in Controlled Studies Conducted Without Sponsor Support

Sample Size (N)	Mean # of Times Used Ecstasy (SD)	MDMA Doses	Mean Age (SD)	Finding by Dose[2,3]	Study
9	63.9 (94.9)	0.75 mg/kg, 1.5 mg/kg	24.0 (3.2)	1.5 mg/kg ↑ VAS Sociable, Friendly	Bedi et al. 2009 [41]
21	15 (23.1)	0.75 mg/kg, 1.5 mg/kg	24.4 (4.9)	1.5 mg/kg ↑ VAS Loving, Playful, POMS Friendly, ↓ fear recognition 0.75 mg/kg ↑ VAS Lonely	Bedi et al. 2010 [82]
8	23.0[4]	75 mg, 125 mg	26.5[4]	125 mg: ↑ ARCI sedation, dysphoria, amphetamine-like ↑ VAS High, body perception changes, confusion, difficulty concentrating ↑ POMS Elation, positive mood 75 mg: ↑ ARCI dysphoria, VAS euphoria, drunken	Cami et al. 2000 [18]
15	110.5 (175.3)	100 mg	21.1 (1.7)	↑ BLMRS Gregarious, Amicable, positive correlation with plasma oxytocin level	Dumont et al. 2009 [663]
36	4-40[1]	0.75 mg/kg, 1.5 mg/kg	24.6 (4.7)	0.75 mg/kg, 1.5 mg/kg ↑ VAS Loving ↓ Cyberball mood & self-esteem effect of social rejection; 1.5 mg/kg ↑ estimate of rejection	Frye et al. 2014 [614]
16	0 (-)	1.7 mg/kg	26.0 (2.5)	↑ EWL Self-confidence, Extroversion	Gamma et al. 2000 [599]
8	5-200[1]	0.5 mg/kg, 1.5 mg/kg	24-39[1]	1.5 mg/kg ↑ VAS Confident	Harris et al. 2002 [20]
16	≤5	125 mg	25.7 (5.5)	↑ VAS Closeness to Others, AMRS Extroversion	Hysek et al. 2011 [582]
48	≤5	125 mg	26.0 (5.0)	↑ VAS Open, Closeness to Others, Talkative	Hysek et al. 2012a [85]

16	≤5	125 mg	25.4 (4.9)	↑ VAS Open, Closeness to Others	Hysek et al. 2012b [221]
16	0	125 mg	26.1 (6.0)	↑ VAS Open, Closeness to Others, Talkative, AMRS Extroversion	Hysek et al. 2012c [224]
16	≤5	125 mg	25.8 (3.3)	↑ AMRS Extroversion, Self-confidence	Hysek et al. 2013 [664]
32	≤5	125 mg	25.0 (3.0)	↑ VAS Open, Closeness to Others, AMRS Extroversion ↑ MET Emotional empathy	Hysek et al. 2014a [55]
16	≤5	125 mg	24.8 (2.6)	↑ VAS Closeness to Others, AMRS Extroversion	Hysek et al. 2014b [541]
8	20.0[4]	1.0 mg/kg, 1.5 mg/kg	25.0[4]	↑ VAS Friendly	Johanson et al. 2006 [665]
14	13.5 (12.0)	0.75 mg/kg, 1.5 mg/kg	25.4 (3.7)	1.5 mg/kg ↑ VAS Friendly, Loving, Sociable	Kirkpatrick et al. 2014a [589]
65	G1: 13.5 (10.6) G2: 18.1 (12.0)	0.75 mg/kg, 1.5 mg/kg	G1: 24.1 (4.1) G2: 23.1 (3.5)	0.75,1.5 mg/kg ↑ VAS Friendly, Loving, Playful, Sociable 1.5 mg/kg ↑ VAS Lonely	Kirkpatrick et al. 2014b [56]
32	SOL: 14.5 (22.2) RAP: 18.4 (13.1) OPP: 20.9 (21.5)	0.5 mg/kg, 1.5 mg/kg	SOL:24.7 (2.7) RAP:25.7 (4.8) OPP:24.5 (3.3)	SOL: 1.0 mg/kg ↑ VAS Insightful RAP: 1.0 mg/kg ↑ VAS Insightful, Loving OPP: 0.5, 1.0 mg/kg ↑ VAS Insightful, 1.0 mg/kg ↑ VAS Loving	Kirkpatrick & de Wit 2015 [612]
8	≥5	1.0 mg/kg, 1.6 mg/kg	21.1 (0.8)	1.6 mg/kg ↑ VAS Closeness to Others	Kolbrich et al. 2008 [17]
14	65.8 (134.5)	75 mg	23.4 (3.0)	↑ POMS Friendliness	Kuypers et al. 2011 [602]
17	18.0 (33.0)	75 mg	21.0 (1.2)	↑ POMS Friendliness	Kuypers et al. 2013 [594]
16	N=13 naïve; N=3 unknown	1.5 mg/kg	27.4 (4.4)	↑ AMRS Extroversion, Self-confidence	Liechti et al. 2000a [576]
14	N=12 naïve; N=2 unknown	1.5 mg/kg	26.0[4]	↑ AMRS Extroversion, Self-confidence	Liechti et al. 2000b [580]
30	≤5	75 mg	24.0 (4.2)	↑ VAS Openness, Trust, Close to Others	Schmid et al. 2014 [587]

12	14.5[4]	1.0 mg/kg, 2.0 mg/kg	22.3[4]	2.0mg/kg ↑ VAS Friendly, Social, Talkative	Tancer and Johanson 2003 [22]
8	28.6[4]	1.5 mg/kg	23.9[4]	↑ VAS Talkative, Friendly, not effected by fluoxetine co-admin	Tancer and Johanson 2007 [579]
17	72.4[4]	75 mg	22.8 (2.8)	↑ POMS Friendliness	van Wel et al. 2012 [86]
101	13.3 (10.5)	0.75 mg/kg, 1.5 mg/kg	24.1 (4.2)	↑ VAS Playful, Loving	Wardle et al. 2014 [34]
36	10.2 (8.2)	0.75 mg/kg, 1.5 mg/kg	24.6 (4.7)	↑ VAS Loving	Wardle and de Wit 2014 [35]

Source: [661, 662]

[1] These studies reported range (min-max) in lieu of mean (SD)

[2] ↑ =Drug increased function relative to placebo, ↓ =Drug decreased function relative to placebo

[3] ARCI=Addiction Research Center Inventory, AMRS=Adjective Mood Rating Scale, FERT=Facial Emotion Recognition Task, BOLD=Blood Oxygen Level Dependent, MET=Multifaceted Empathy Test, SVO=Social Value Orientation Test, mFER=morphed Facial Emotion Recognition Task, RMET=Reading the Mind in the Eyes Test, MASC=Movie for the Assessment of Social Cognition, MJT=Moral Judgment Task, DANVA=Diagnostic Analysis of Nonverbal Accuracy, DEIT=Dynamic Emotional Identification Task, IPT=Interpersonal Perception Task (Modified), POMS=Profile of Mood States, VAS=Visual Analog Scale, G1= Group 1, G2=Group 2

[4] SD not presented in original publication

In a study conducted without sponsor support of 22 individuals (mean age 23.6) with a history of stimulant drug use (more than six times) and previous Ecstasy use (more than 3 times) in a double-blind randomized study, participants were asked to identify 2.0 mg/kg MDMA and serotonergic drug meta-chlorophenylpiperazine (mCPP), which has both serotonin releasing and post-synaptic effects. At 1 to 2.1 mg MDMA, 80% of participants identified MDMA as an empathogen or hallucinogen and only 20% identified MDMA as a stimulant [615]. In contrast, results were mixed with 0.25 to 0.75 mg/kg mCPP, with results varying from hallucinogen to stimulant to sedative depending on the dose. On the "drug liking" VAS, 1.6 mg/kg ($p<0.004$) and 2.1 mg/kg MDMA ($p<0.008$) were significantly higher than placebo, whereas mCPP ratings were not significantly higher than placebo at any dose [615]. In another study in a sample of 74 largely drug-naïve participants receiving MDMA in a controlled laboratory setting, Liechti and colleagues stated that "none of the participants expressed any interest in taking MDMA as a recreational drug" after receiving MDMA [21]. Collectively, these findings support the interpretation that MDMA received in controlled settings is inherently different than MDMA taken in recreational settings, and abuse liability of MDMA-assisted psychotherapy should be evaluated in its intended setting and population for clinical use.

Drug Discrimination and Stimulant Comparison

The abuse liability of MDMA has been investigated in healthy volunteers utilizing a drug discrimination paradigm in two studies. The first study was in healthy nondependent volunteers with moderate MDMA experience (mean age 22.3) with a history of stimulant drug use (more than 6 times) and previous Ecstasy use (mean 14.5 times) comparing placebo, 10 mg and 20 mg d-amphetamine, 0.5 mg/kg and 0.75 mg/kg mCPP and 1.0 mg/kg and 2.0 mg/kg MDMA in a within-subject design (N=12). In this study, MDMA and d-amphetamine had similar reinforcing effects, and both were more than the effects of mCPP [22]. In humans trained to discriminate in a three-way procedure among 20 mg d-amphetamine, 0.75 mg/kg mCPP, and placebo, both 1.0 mg/kg and 1.5 mg/kg MDMA was reported by half the participants to be like amphetamine and half like mCPP (N=22). Individuals who identified MDMA to be more like amphetamine were more sensitive to the subjective effects of all drugs, and they were more experienced with using Ecstasy and stimulants prior to the study [665]. Table 26 below presents a summary of studies with direct comparisons of MDMA vs. stimulants. Seven of ten studies found differences between MDMA vs. stimulants, with doses of 2.0 mg/kg MDMA and higher having more similar effects to stimulants.

Table 26: Summary of Selected Effects in Controlled Clinical Studies Comparing MDMA and Stimulants Among Healthy Volunteers Conducted Without Sponsor Support

Pre-study Ecstasy Use History			During Controlled MDMA Administration		During Controlled Stimulant Administration	
Sample Size (N)/ Study	Mean # of Times Used Ecstasy (SD)	Mean Age (SD)	MDMA Doses Tested	Finding by Dose[c]	Stimulant Doses Tested	Finding by Dose[c]
8/ Cami et al. 2000 [18]	23.0[c]	26.5[c]	75 mg, 125 mg	125 mg: ↑ ARCI sedation, dysphoria, amphetamine-like ↑ VAS High, body perception changes, confusion, difficulty concentrating ↑ POMS elation, positive mood 75 mg: ↑ ARCI dysphoria ↑ VAS euphoria, drunken	*d*-Amph 40 mg	↑ ARCI amphetamine-like, energy, intellectual efficiency ↓ ARCI sedation
21/ Bedi et al. 2010 [82]	15 (23.1)	24.4 (4.9)	0.75 mg/kg, 1.5 mg/kg	1.5 mg/kg ↑ POMS Friendly, ↓ fear recognition No effect on VAS Social	Meth 20 mg	No effect on fear recognition or POMS Friendly ↑ VAS Social
13/ Bedi et al. 2014 [33]	2 (-)	18-38[a]	0.75 mg/kg, 1.5 mg/kg	1.5 mg/kg ↑ social words	Meth 20 mg	No effect on social words
16/ Hysek et al. 2014b [541]	≤ 5	24.8 (2.6)	125 mg	↑ VAS Closeness to Others, AMRS Extroversion ↓ recognition: negative emotions	Methylph 60 mg	↑ recognition: negative emotions
8/ Johanson et al. 2006[665]	20.0[c]	25.0[c]	1.0 mg/kg, 1.5 mg/kg	↑ VAS Friendly	*d*-Amph 20 mg	↑ VAS Friendly
11/ Kirkpatrick et al. 2012[42]	2.1 (1.8) per month	29.3 (50)	100 mg	↑ VAS Social, Talkative	Meth 20 mg 40 mg	20 mg ↑ VAS Social 40 mg ↑ VAS Social, Talkative
30/ Schmid et al. 2014 [587]	≤ 5	24.0 (4.2)	75 mg	↑ MET Emotional empathy for positive situations ↓ recognition: sadness	Methylph 40 mg	No effect on emotional empathy for positive situations or recognition of sadness
12/ Tancer, Johanson	14.5[c]	22.3[c]	1.0 mg/kg, 2.0 mg/kg	2.0 mg/kg ↑ VAS Friendly, Social,	*d*-amph 10 mg,	20 mg ↑ VAS Friendly

2003 [22]				Talkative	20 mg	
30/ Schmid et al. 2015 [666]	≤ 5	24.0 (4.2)	75 mg	No effect on ratings of erotic images	Meth 40 mg	↑ ratings of erotic images
11/Marrone et al. 2010[667]			100 mg	No effect on speech quantity ↓ fluency	Meth 20 mg 40 mg	↑ speech quantity, fluency

A dose of 100 mg MDMA was directly compared to 20 mg and 40 mg methamphetamine in a placebo-controlled blinded in-patient study measuring pharmacokinetics, physiological effects, and subjective effects (N=11) [42]. The study was in healthy non-dependent volunteers (mean age 29.3, SD:50) with current stimulant (4.2 days/month) and Ecstasy use (2.1 days/month). Both drugs had a similar time course of effects with oral administration. Plasma levels peaked at 3 hours and declined over the 24-hour period post-administration, with minor levels of drug remaining above baseline in plasma at the end of this period. Both drugs enhanced cardiovascular parameters, ratings of stimulation, euphoria, and mood, and decreased food intake. Methamphetamine, but not MDMA, caused significant residual pulse and DBP elevation at the end of the 24-hour period ($p<0.01$). MDMA did not enhance performance, indicating the absence of this contributor to reinforcing effects, in contrast to methamphetamine. Methamphetamine produced primarily positive effects (Good Drug Effect, Stimulated, Desire to Take Again, Drug Liking), whereas MDMA had some positive (Good Drug Effect, Stimulated) and some negative effects (Bad Drug Effect, Can't Concentrate, Tired, Sleepy). Only methamphetamine disrupted sleep, objectively measured via Actigraphy, and increased tiredness. MDMA did not disturb sleep, and instead facilitated ability to more readily fall asleep. As most participants were unable to correctly identify the drug received, and important confound is that experienced Ecstasy users may have based their opinions about MDMA on material of low purity and unknown dose. The sponsor has been given permission to access primary data for this study under IND #074039. Taken together, these observations and other studies support distinct differences in subjective and reinforcing effects, supporting a lower abuse liability for MDMA than stimulants.

Prevalence of Dependence

There have been no reports of MDMA dependence developing after participation in controlled MDMA studies. In the absence of drug dependence studies on MDMA, a summary of Ecstasy dependence studies is presented. Ecstasy is purported to contain MDMA, but in the majority of pills submitted for anonymous testing, no MDMA is found and/or impurities abound. Some adulterants, such as amphetamines, that are commonly found in Ecstasy tablets may be responsible for the dependence and cravings associated with Ecstasy [668]. Research of Ecstasy dependence comes from a combination of published studies with assessment of symptoms based on the Composite International Diagnostic Interview, the DSM-4, and/or the Severity of Dependence Scale [669]. One study with a non-representative sample (N=173) including participants recruited from substance abuse programs reported 30% had used Ecstasy and of these, 43% met Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) criteria for dependence (N=52) [670]. In a large Australian sample (N=329), approximately 25% of polydrug users wanted to reduce their Ecstasy use and 20% had received treatment for an

Ecstasy-related problem, although this sample likely had "an over-representation of chaotic intravenous polydrug users [671].

In a study of self-reported cravings in Ecstasy users utilizing an 8-item questionnaire (N=169), a negative mean score for participants exposed to Ecstasy-related cues was obtained, indicating that participants disagreed with statements reflecting craving on average. In a subscale analysis, about 50% of survey participants agreed on some level with two of eight statements that supported the craving to use Ecstasy after exposure to Ecstasy-related cues, suggesting that some respondents may experience a low level of craving for Ecstasy [668]. It also appears that Ecstasy 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 [189, 309, 672]. Based on two structural analyses, Ecstasy dependence is bifactorial [673]. Although Ecstasy dependence does have a compulsive use factor as well as an escalating use factor, withdrawal symptoms do not include significant physical symptoms such as those occurring with alcohol, cocaine, methamphetamine, opioids, and tobacco [674, 675]. In a prospective longitudinal study conducted over an average of 42 months in a representative sample of Munich residents aged 14 to 24 (N=2446), only 1.0% were diagnosed with Ecstasy abuse and 0.6% with dependence. A substantial decline in use factors was noted 12+ months later, suggesting that Ecstasy use is a self-limiting transient phenomenon in many cases [676]. Features of Ecstasy abuse and dependence in healthy human volunteers are consistent with nonclinical findings in self-administration studies of moderate abuse liability that is greater than that for serotonergic hallucinogens, but less than that for stimulants (see Section 4.3.5.3 Abuse Potential).

When reviewing the effects of MDMA in a sample of 74 largely drug-naïve participants in a study conducted outside of sponsor support, 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 [21]. When assessed in terms of willingness to choose money over receiving the drug, participants previously experienced with Ecstasy provided similar responses to 2 mg/kg MDMA and 20 mg d-amphetamine, a sign of having reinforcing effects [615]. A study that enrolled participants with a history of Ecstasy use (4 to 40 occasions) found that only self-reported feelings of playfulness were associated with participants' desire to take MDMA in a controlled research setting [35].

In addition to the extensive published clinical and nonclinical literature on the abuse liability potential associated with MDMA, the sponsor has collected self-reported Ecstasy use data at long-term follow-up and assessed the AEs for signals of abuse. At screening participants who met DSM-4 criteria for active substance abuse for 60 days prior to enrollment were excluded from participation in all but one study, where active substance abuse for 180 days prior to enrollment was excluded (MP-4). Participants who had used Ecstasy more than five times within the past 10 years prior to enrollment were also excluded. As a part of the Informed Consent process, study staff informed participants about the difference between Ecstasy and MDMA used in research studies. Table 27 below summarizes self-reported Ecstasy use data (recreational drug purported to be MDMA, unknown purity and dose) pre-study at least 6 months prior to study entry vs. long-term follow-up at 12+ months in Phase 2 PTSD clinical trials. Participants were

encouraged to report use honestly under coverage of a Certificate of Confidentiality from FDA.

Table 27: Pre-Study Ecstasy Use Compared to Ecstasy Use Based on Long-term Follow-up Questionnaire After All Participants Received Two to Three Blinded or Open-label Active Dose MDMA-Assisted Psychotherapy for Treatment of PTSD

Pre-study Ecstasy Use				Long Term Follow-Up Post MDMA			
	Enrolled N	People Reporting Pre-study Use Pre-study N (%)	Mean # of Times Used (SD)	LTFU N	People Reporting Post-Study Use N (%)	Mean # of Times Used (SD)	Context of Use
MP1							
	23	10 (43.5%)	2.0 (1.25)	19[a]	1 (5.3%)	1 (-)	Attempted Therapeutic
MP2							
	14	1 (7.1%)	3.0 (-)	11[b]	0 (0.0%)	-	-
MP4							
	6	0 (0.0%)	-	6	0 (0.0%)	-	-
MP8							
	26	6 (23.1%)	2.7 (1.21)	24	2 (8.3%)	1 (-)	Attempted Therapeutic; Recreational
MP9							
	10	2 (20.0%)	1.0 (0.00)	8	2 (25.0%)	1.5 (0.71)	Attempted Therapeutic; Recreational
MP12							
	28	13 (46.4%)	2.6 (1.71)	24	3 (12.5%)	1.3 (0.58)	Attempted Therapeutic; Recreational
All Studies Pooled							
	107	32 (29.9%)	2.3 (1.43)	92	8 (8.7%)	1.3 (0.49)	Attempted Therapeutic; Recreational

[a] CAPS data available from N=16 only, questionnaire available from N=19
[b] One subject died prior to completing long-term follow-up due to progression of cancer.

In sponsor-supported PTSD studies in 107 participants treated with MDMA-assisted psychotherapy in a controlled clinical setting, 29.9% (32 of 107) of participants had tried Ecstasy at least 6 months prior to enrollment, with U.S. samples demonstrating a higher prevalence of use than international studies. Participants reported using Ecstasy an average (SD) of 2.3 (1.43) times pre-study at least 6 months prior the study. At long-term follow-up, 8.7% of participants (8 of 92) reported use across studies (see Table 27). Six of the eight participants had used Ecstasy prior to the study. See also [1]. Of these participants, most were attempting to recreate a therapeutic experience, and none indicated a desire to repeat this. In addition to self-report data, urine drug screens specific for MDMA were performed at random and two, six and 12 months after the final Experimental Session during one study (MP-2, N=12). All were negative, supporting the observation that study participants did not seek out MDMA or Ecstasy after taking part in the study [5]. In addition to data on Ecstasy use at follow-up, AEs were reviewed across Phase 2 studies, the sponsor found a low rate of clinically significant AEs supporting drug dependence, intentional drug misuse, substance abuse, and (<2%) of secondary terms that reflect acute intoxication. One instance of "drug abuse" was reported in study MDA-1 in a population with anxiety associated with life-threatening illness. This AE referred to a single nondependent use of a hallucinogen, which MedDRA coding places under the preferred term 'drug abuse" but does not indicate a substance use disorder.

Data drawn from sponsor-supported studies suggests that MDMA has low abuse liability when given within a controlled, psychotherapeutic setting.

Conclusions on Safety of MDMA

Safety data from studies in controlled research settings show that MDMA produces sympathomimetic effects that include statistically significant, self-limiting increases in body temperature, heart rate, and blood pressure that are likely to be transient and well tolerated by healthy individuals [3-5, 17, 19-21, 39-44, 81, 542]. Risks posed by elevated blood pressure are addressed in clinical trials by excluding candidates with a history of cardiovascular or cerebrovascular disease or with pre-existing uncontrolled hypertension and by monitoring blood pressure and pulse during MDMA-assisted Experimental Sessions. Common reactions from MDMA research studies included anxiety, fatigue, muscle tightness, and nausea, which were transient and diminished as drug effects waned during treatment sessions and over a next 24-hour period. In studies conducted with and without sponsor support in controlled clinical settings, with individuals exposed to MDMA, there have been no published or reported unexpected SARs to date, and expected SARs have been rare and non-life threatening. One subject to date experienced an expected SAR (increased ventricular extrasystoles, reported in Study MP-8) in MAPS-sponsored clinical trials. SUSARS occur infrequently in the program and the sponsor is monitoring any SUSARs and once definitive information is available to determine if any SUSARs should be upgrade to SARs, the IB will be updated with this information.

7.0 Summary of Data and Guidance for the Investigator

MDMA is a psychoactive compound that affects mood, perception, and increases prosocial feelings. The sponsor is investigating use of this compound as an adjunct to psychotherapy for treating PTSD, social anxiety in people on the autism spectrum, and anxiety related to a life-threatening illness. Researchers with and without sponsor support have conducted in vitro and in vivo non-clinical and clinical studies with MDMA, and additional clinical trials are ongoing. Currently, MDMA is listed as a Schedule I controlled substance in the U.S. and is not permitted for medical use outside of research settings. Psychotherapists in the U.S. began to use MDMA as an adjunct to psychotherapy in the mid to late 1970s, and narrative accounts describe therapeutic use with an estimated 500,000 doses of MDMA administered during psychotherapy sessions in North America prior to its scheduling [49, 307]. MDMA has been administered to more than 1431 people in controlled research settings and 279 participants in the development program as of April 30, 2020. These studies have demonstrated that MDMA can be safely administered to people with PTSD in a controlled clinical setting.

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 with rapid onset in some participants. A limited number of exposures to MDMA, spaced approximately 1 month apart at active doses between 80 to 125 mg, are sufficient to obtain therapeutic outcomes. This intermittent dosing mitigates AE frequency and improves the risk/benefit ratio of MDMA, which may provide a significant advantage over medications that require daily dosing. Based on the current state of scientific knowledge and the risk/benefit profile of therapeutic doses of MDMA, the sponsor

concludes that it appears favorable to continue the clinical development of MDMA as a medicine used as an adjunct to psychotherapy.

7.1 Pharmacology

The pharmacology of MDMA is complex, it activates multiple signaling cascades in the body. The formulation of the Investigational Product in Phase 2 studies consists of a gelatin capsule consisting of white crystalline racemic MDMA, at doses ranging from 12.5 mg to 150 mg, compounded with alpha-lactose, and administered orally. The Investigational Product in use in Phase 3 studies consists of hydroxypropylmethylcellulose (HPMC) capsules of 40 and 60 mg MDMA hydrochloride with the excipients mannitol and magnesium stearate (and matching placebo capsules of mannitol and magnesium stearate). Due to a wide range of responses to identical mg/kg dosing between individuals, possibly as a result of inconsistent relationship between body weight and pharmacodynamic activity, the sponsor's human trials use doses between approximately 1 and 4 mg/kg (active doses range from 75 mg to 225 mg cumulative with supplemental dosing, assuming a 70 kg individual) to achieve a more consistent response between participants. In humans, onset of effects occurs approximately 30 to 60 minutes after administration, and peak effects occur 75 to 120 minutes after administration. Duration of effects lasts 3 to 6 hours, which extends to 6 to 8 hours with supplemental dosing. In the ongoing and planned Phase-3 clinical trials, a fixed dose of 80 mg (MDMA or placebo) is administered in the first Experimental Session. A flexible dose of 80 to 120 mg is administered in the second and third Experimental Sessions optionally followed by either a 40 to 60 mg optional supplemental dose to increase the duration of action.

The pharmacokinetics properties of MDMA in humans have been characterized using oral doses up to 150 mg MDMA in humans. MDMA disposition in the body follows nonlinear pharmacokinetics. MDMA is metabolized in the liver by several enzymes. Active doses of MDMA may autoinhibit CYP2D6 function for an extended period, with function normalizing up to 10 days post-MDMA. The enzymes CYP1A2, COMT, and MAO are also be involved in the metabolism of MDMA. MDMA is metabolized by N-demethylation to MDA. The parent compound and MDA are further O-demethylated to HHMA and HHA, respectively. Both HHMA and HHA are subsequently O-methylated mainly to HMMA and HMA. These four metabolites, particularly HMMA and HMA, are known to be excreted in the urine as conjugated glucuronide or sulfate metabolites. The elimination half-life of active MDMA doses is 7 to 9 hours.

MDMA is a triple monoamine reuptake inhibitor, which concomitantly promotes carrier-mediated release, inhibits reuptake, and extends duration of serotonin, norepinephrine, and dopamine in the synaptic cleft to increase serotonergic, noradrenergic, and dopaminergic neurotransmission. Additionally, MDMA appears to alter the conformation of the transporters, enabling monoamines to diffuse out of the neuron rather than being actively transported into the presynaptic neuron. MDMA was found to compete with monoamines for sites on the VMAT2, suggesting MDMA also promotes active release of monoamines from vesicular stores, in addition to inhibiting reuptake. MDMA extends the presence of monoamines in the synaptic cleft by inhibiting MAO-A, an enzyme that breaks down monoamines in the synapse. MDMA has self-limiting subjective and physiological effects. MDMA administration is contraindicated in patients taking MAOI

medications. Fatalities have been reported after the combination of MAOIs and MDMA in Ecstasy users. Co-administration with an SSRI may eliminate or greatly attenuate the effects of MDMA, and these medications should be tapered in line with the investigator's clinical judgment and an approved study protocol.

Brain imaging studies report that MDMA has been shown to acutely decreases activity in the left amygdala and increases activity in the prefrontal cortex. The chief mechanism behind its therapeutic effects is likely to be serotonergic, along with some norepinephrine and to a minor extent dopamine-mediated effect. Indirect, but potentially significant effects of MDMA include association with release or elevated levels of the hormones cortisol, oxytocin, prolactin, and AVP. MDMA likely stimulates secretion of oxytocin into peripheral blood via indirect activation of 5HT1A, 5HT2C, and 5HT4 receptor subtypes, as well as AVP secretion via activation of 5HT2C, 5HT4, and 5HT7 receptor subtypes. Both oxytocin and AVP are implicated in the widespread regulation of behavioral aspects of mood and act on different target organs to modulate physiological functions in the body. Taken together, MDMA has a diverse array of pharmacodynamic effects in animals and humans.

7.2 Toxicology

The toxicity of MDMA has been investigated in numerous animal and in vitro studies published in peer-reviewed journals. 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. LD50 varies between different strains of the same animal species, across the sexes, housing conditions, environmental conditions, social interactions with cohabiting animals, exercise levels, and water supply. Most preclinical toxicology data is derived from repeated dose studies. Nonclinical researchers typically selected doses through use of interspecies scaling, a method of modeling human-equivalent doses in other species, however pharmacokinetic and pharmacodynamic data have questioned the applicability of allometric interspecies scaling as an appropriate means of approximating human-equivalent doses. As a result, most research in rodents and primates used doses of MDMA that supersede human-equivalent doses, thus translation to human recreational and therapeutic use is limited. Additionally, many published epidemiological and observational studies of people who use Ecstasy are also subject to the limitations in interpretation due to unknown purity, dose, and quantity of MDMA existing in Ecstasy tablets used in naturalistic settings.

Extensive preclinical toxicological studies report that high or repeated doses of MDMA can increase locomotor activity and signs of serotonin syndrome, which can damage serotonergic axons originating in the brainstem dorsal raphe nuclei, likely through oxidative stress, and this damage is associated with decreases in serotonin production, serotonin metabolites, and SERT site densities. While these findings are consistent across studies, studies in people reporting low to moderate Ecstasy use do not report an increase in a biological marker of neuronal injury, and only one of three studies in heavy users detected this marker. Retrospective studies in Ecstasy users have found contradictory effects on visual and verbal memory, planning and making decisions, and some types of visual processing. An uncontrolled prospective study of moderate Ecstasy users failed to find changes in SERT sites or signs of neuronal injury; slight changes in cerebral blood

flow (CBF) in the dorsolateral PFC were found. In the same study, Ecstasy users showed less improvement on a memory task than non-users. Taken together, these findings suggest possible indications of cumulative toxicity in chronic high dose dosing regimens but not as administered in clinical trials.

MDMA has not been demonstrated to be genotoxic. Consistent with this, despite very high doses of MDMA being tested in preclinical studies, none have reported carcinogenic effects. Risks posed to pregnant women by MDMA are not known. Two of three studies of Ecstasy users suggest that use of Ecstasy and other drugs during pregnancy may be associated with some abnormalities at birth, delays in mental and motor development, but not language or emotional development. Rodent fertility, reproductive, and developmental toxicity studies with MDMA have generally found no abnormalities in gestational duration, neonatal birth weights, or physical appearance when exposure occurs during organogenesis through lactation. However, one study of fertility and developmental toxicity in mice found evidence of toxicity at doses 5 mg/kg s.c. and above when exposure occurred in both genders of a breeding pair at some point between spermatogenesis/ovulation through closure of the hard palate. The results of several behavioral tests indicate that developmental MDMA exposure combined with adult exposure in rats may interfere with some aspects of learning, including visual-spatial memory, and time spent with a novel object. MDMA exposure in utero exacerbated hyperthermic response to a subsequent dose to MDMA. A study in neonatal rats suggests two distinct critical periods wherein repeated MDMA doses affected learning versus acoustic startle. In conclusion, MDMA might possess weak reproductive or developmental toxicity with a daily toxic chronic dosing regimen, in contrast to six or less exposures, spaced 1 month apart, tested in clinical trials. All sponsor-supported trials of MDMA exclude pregnant and lactating people, and people who are able to become pregnant must have a negative pregnancy screen before undergoing each Experimental Session and must agree to use birth control during the period of the protocol. If any subject becomes pregnant during study participation, the sponsor and clinical investigator will follow the pregnancy to outcome.

There are reports of morbidity and mortality in individuals who use Ecstasy (material represented as containing MDMA, as defined above) around the world in unsupervised and uncontrolled settings, usually involving poly-drug use (see Table 3 in Section 5.1 Serious Reports of Incidents, Mortality, and Morbidity). These events are relatively rare given the prevalence of Ecstasy use, estimated to be approximately 20 million worldwide. The most common adverse effects in Ecstasy and poly-drug use described in published case reports include hyperthermia, psychiatric problems, hepatotoxicity secondary to hyperthermia, and hyponatremia (see Section 4.3 Toxicology and Section 5.1 Serious Reports, Morbidity, and Mortality). Published reports examining emergency department admission after Ecstasy use cite anxiety and panic reactions as the most frequent reason for admission. Fatal dysrhythmias have been reported following heavy MDMA use, resulting in ventricular fibrillation and asystole. Individuals with underlying cardiac and/or pulmonary disease and preexisting conditions such as Wolff-Parkinson-White syndrome are especially at risk for heart failure and fatal arrhythmias when using MDMA. Set and setting likely play a role in the development of some Ecstasy-related adverse reports, such as vigorous exercise, lack of attention to somatic cues, and too little or too much hydration combined with pharmacological action on AVP, resulting in

hyperthermia or hyponatremia. Even if ambient temperature does less to moderate the effects of MDMA on body temperature in humans than originally believed based on animal studies, other environmental and behavioral factors, as those related to vigorous exercise, may be involved. Overall, the risks of serious events appear to be minimal in controlled settings with adequate screening according to eligibility criteria defined in study protocols. With the exception of one cardiac SAR (increase in ventricular extrasystoles), none of these events have occurred within the context of human clinical studies with MDMA, likely due to careful screening for pre-existing risk factors and limited exposure in a controlled clinical setting.

7.3 Physiological Effects

7.3.1 Adverse Events

Overall, adverse effects of MDMA were modest and generally have not been associated with serious discomfort in healthy volunteers or in subjects in MAPS-sponsored Phase 2 studies. Risks posed by sympathomimetic effects of MDMA treatments are addressed in MAPS' clinical trials by excluding people with pre-existing cardiovascular disease, cerebrovascular disease or uncontrolled hypertension, and by monitoring blood pressure, body temperature, and pulse. Common reactions reported in clinical trials were transient and diminished as drug effects waned during the MDMA-assisted session and over the next 24 hours. Once the drug fully cleared from the body, 3 to 4 days post-treatment, most reactions diminished. In the PTSD studies, anxiety and fatigue were the most commonly reported AE's across all treatment groups. Greater than 5% of both blinded and open-label active MDMA dose group participants reported muscle tightness and nausea. The only SAEs that were reported by more than one participant, which occurred in the blinded 75 to 125 mg MDMA group, were depressed mood and panic attack. There were several SRRs that were not reported in the placebo group but were reported in either the active blinded 75 to 125 mg MDMA or open-label 100 to 150 mg MDMA groups: dry mouth, diarrhea, heavy legs, impaired judgement, and nystagmus. For other SRRs, ≥ 10% of participants in the active MDMA dose groups reported the following reactions were not resolved by 7-day follow-up after Experimental Session: anxiety, fatigue, difficulty concentrating, increased irritability, insomnia, and low mood.

There have been reports of morbidity and mortality in individuals who use Ecstasy (material possibly containing MDMA) in uncontrolled settings outside of research studies, usually involving poly-drug use and moderate to intense physical activity. Individuals experiencing these adverse effects have not been carefully screened based on eligibility criteria and are likely to have pre-existing medical conditions or underlying cardiac and/or pulmonary disease that influence metabolism and disposition of MDMA in the body. These events are relatively rare given the prevalence of Ecstasy use, estimated to be in the millions worldwide. The most common adverse effects in sponsor-initiated trials included anxiety, fatigue, muscle tightness, and nausea (see Table 10). Overall, the risks of SARs have been addressed and constrained by limited exposure and drug administration in controlled settings with adequate screening according to eligibility criteria defined in study protocols. To date, only one SAR (exacerbation of pre-existing ventricular extrasystoles) has been reported within the context of MAPS-sponsored clinical studies. The possibly drug-related expected of exacerbation of pre-existing

ventricular extrasystoles occurred during open-label treatment with 125 mg MDMA, which resolved with full recovery to baseline after the Investigational Product's effects ceased. The subject was hospitalized for observation and recovered fully after the event, with no cardiac damage.

7.3.2 Suicidal Ideation and Behavior

There is high incidence of suicidal ideation and behavior in populations of people with PTSD, especially those suffering from chronic, treatment resistant PTSD. To determine if suicidal ideation and behavior worsens or improves after treatment in MAPS-sponsored trials, the C-SSRS is administered repeatedly throughout MAPS sponsored clinical trials. Due to the nature of the therapeutic method, wherein a person may re-experience emotions associated with the traumatic event in order to reprocess the memory in a new, therapeutic way, thoughts of ending one's life may surface during this process. In MAPS-sponsored clinical trials C-SSRS scores have escalated during the Preparatory Sessions (before any drug administration), which is thought to be a result of preparatory discussion of traumatic experiences, and/or of participants tapering off long-prescribed medications, such as SSRIs and benzodiazepines. Withdrawal of these drugs is known to induce suicidal ideation or behavior in some people. During both non-drug and MDMA-assisted psychotherapy sessions, participants are asked to think about and discuss their experiences, thoughts, and emotions related to their condition. They may experience intense emotional responses to recalling and speaking about this material. As MDMA is only administered in combination with psychotherapy, the distress associated with psychotherapy is unavoidable, and is considered a necessary part of the therapeutic process that requires proper facilitation and support from therapists.

Overall the incidence of serious suicidal ideation or behavior in sponsor-supported studies was low, occurring in only a few participants post-MDMA treatment, and returning to lower scores while participants were closely monitored. As of 30 April 2020, three cases of suicidal ideation and four cases of suicidal behavior were deemed Serious Adverse Events across sponsor-supported Phase 2 and Phase 3 studies. Suicidal ideation was reported in a participant in study MP-8, reported 6 days after treatment with 30 mg MDMA and lasted 6 days, concurrent with increased depressive symptoms triggered by external trauma cues, and was treated with prescription medication and hospitalization. The participant who experienced suicidal ideation later experienced depression that was rated serious and unrelated to the Investigational Product, with the event occurring approximately 9 months after a final Experimental Session. The episode resolved approximately 3 weeks after it developed. Depression in this subject was rated severe. The depression led to hospitalization, and the participant reported full recovery after the episode. In an extension to study MP-1 involving a single, additional administration of 125 mg MDMA for participants exhibiting relapse after completing the study, a participant was hospitalized with major depressive episode and suicidal ideation 9 months after the additional Experimental Session, and fully recovered after this episode. In MAPP1, one participant was hospitalized 9 days after the blinded Experimental Session for expressing a worsening feeling of not wanting to live and with no plan or intent of self-harm. The participant was prescribed Lexapro by the hospital doctor, released from hospital, and reported feeling better.

As for the four SAEs of suicidal behavior, two events were reported in one participant in the ongoing, placebo-controlled study MAPP1, and one event in one person in the open-label study MP16, and one in study MP-2. In MP-2, prior to the collection of formal suicidal ideation with C-SSRS, one participant was hospitalized for suicidal behavior that allegedly developed after a conflict with her ex-husband 2 weeks prior to drug administration, indicating that suicidal ideation and behavior can occur at baseline prior to drug administration. This subject fully recovered and went on to participate in the study. In the case occurring in MP16, the therapists learned of a recent suicide attempt during an Integrative Session, possibly arising from apprehension about the study ending. The participant was admitted to the ER overnight, and fully recovered in the subsequent day. In the first of the two events in the participant in the ongoing, placebo-controlled MAPP1 study, the participant ingested a combination of over the counter medications, and acknowledged suicidal ideation, but followed instructions not to consume alcohol. This was considered an occurrence of testing the therapists, but after discussion was coded as a suicide attempt. The second event occurred 2 months later, still within the blinded portion of the MAPP1 study.

Given that people suffering from severe PTSD are known to experience suicidal ideation and behavior, it is difficult to identify a single cause of the increase in suicidal thinking or behavior (i.e., exacerbation of PTSD symptoms related to medication withdrawal or to the psychotherapeutic process, or from MDMA effects). A large percentage of people enrolled in the studies reported suicidal ideation and behavior during sometime in their lives prior to study enrollment, which may reflect a manifestation of PTSD or co-morbid affective disorders. There were no reports of positive suicidal ideation or behavior after the first Experimental Session in participants with a life-threatening illness and only few incidences, none serious, of positive ideation in adults on the autism spectrum during the study. When positive serious ideation or behavior occurred after study enrollment, the investigators made follow-up observations of C-SSRS to ensure subject safety and tracked scores until they returned to non-serious levels.

Therapy teams minimize risks by carefully evaluating all participants to determine if there is a current risk of suicidal behavior. Participants with a history of suicide attempts are not excluded unless significant risk of suicidal behavior is present at the time of Screening. Participants are enrolled according to the Eligibility Criteria based on the clinical judgment of the site physician, therapy team, and Medical Monitor.

7.3.3 Vitals

MDMA is responsible for a series of dose dependent physiological effects due to enhanced neurochemical release of serotonin, norepinephrine, and dopamine, and for indirect effects on hormone secretion, including oxytocin and AVP, which act on different target organs to modulate physiological functions in the body. Active doses of MDMA (75 mg to 150 mg), alone or followed by a supplemental half-dose 1.5 to 2.5 hours later, produced statistically significant but transient, self-limited increases in blood pressure, heart rate, and body temperature that were well tolerated by healthy individuals. The elevation of blood pressure and increased heart rate produced by MDMA, like that produced by other sympathomimetic drugs, can lead to additional complications in people with pre-existing medical conditions that increase risk. In combination with

clinical signs and symptoms, elevations in pulse and blood pressure can also lead to cardiac events, such as arrhythmias.

Literature on epidemiological studies suggest a relationship between Ecstasy dose and likelihood of hyperthermia. Hyperthermia has occurred in people using Ecstasy in unsupervised and non-medical conditions, and though rare, is one of the most frequently reported serious adverse reports occurring in Ecstasy users. Environmental and behavioral factors, as well as thyroid dysregulation, may contribute to case reports and preclinical findings of hyperthermia. Findings from previous Phase 1 trials indicate that MDMA administered in a controlled setting produces a statistically but not clinically significant increase in body temperature (mean elevation of 0.6°C). Unlike rodents, ambient temperature does not affect elevation in core temperature in humans. Controlled clinical settings have been sufficient to manage body temperature in humans.

Body temperature greater than 1°C above baseline was detected after any dose of MDMA, in 44% of participants with PTSD, with most of these cases observed in sessions with 125 mg MDMA. In individuals with autism or a life-threatening illness, 29% and 50% of subject respectively exhibited elevated body temperature after 100 to 125 mg MDMA (blinded). In contrast, in 20% of participants that were administered inactive placebo had an elevation of body temperature above cut-off in PTSD studies. Both peak and longest duration of body temperature elevation were observed in the 125 mg MDMA group. Across all indications, the maximum peak reading was 38.7°C. Vital signs in sponsor-supported Phase 2 studies presented above suggest a dose-dependent action on SBP and pulse, which is consistent with the literature on healthy volunteers. Body temperature and DBP do not appear to be strongly related to MDMA dose. No participants receiving MDMA in sponsor-supported clinical trials have required any clinical interventions for elevated vital signs, as all values returned to normal as the effects of MDMA diminish.

Participants enrolled in controlled Phase 1 single dose MDMA trials conducted without sponsor support had elevations above a pre-determined cut-off of at least 140/90 mmHg (approximately 5% per trial). All participants in a subsequent trial in a separate sample given a regimen of 50 mg followed by 100 mg 2 hours later had blood pressure elevations above 140/90 mmHg. Based on the literature, effects of the initial dose of MDMA on blood pressure and heart rate are expected to have a linear dose-response relationship, and the supplemental dose may have an effect on SBP elevation. SBP above 160 mmHg, a pre-determined cut-off for more frequent readings, was detected in 32% of blinded Experimental Sessions where MDMA was administered at any dose in studies of PTSD, 0% of participants on the autism spectrum, and 75% of participants that received 125 mg (blinded) with a life-threatening illness. Most of these instances occurred with the 125 mg MDMA dose group. Both peak and longest duration of blood pressure elevation were also observed in the 125 mg MDMA group. Maximum SBP observed across studies was 200 mmHg after a 125 mg dose. MDMA doses of 40 mg and greater were associated with SBP above 160 mmHg for some people, supporting a dose dependent effect of MDMA on blood pressure. DBP above 110 mmHg was observed in 7% and 37.5% of participants after 75 mg or 125 mg blinded MDMA in participants with PTSD or a life-threatening illness, respectively. All except one of these instances occurred with the 125 mg MDMA dose. Candidates with controlled hypertension were excluded from

participation in all but one of sponsor-supported studies to limit cardiovascular risk during treatments. In MP-8, the only study that did enroll a sub-group of participants with controlled hypertension, SBP above 160 mmHg was detected in 75% (3 of 4) of participants and 67% (8 of 12) of Experimental Sessions where MDMA was administered to this sub-group. The prevalence of these elevations appears higher in this sub-group than the overall sample, although the prevalence could decrease in a larger group. Pre-drug SBP was typically higher in this sub-group, and peak SBP of these participants was typically at the upper end of the range of the overall sample. Final SBP readings remained 8 mmHg higher than pre-drug SBP readings in one subject that received 75 mg MDMA. The single subject with extended duration of SBP elevation had a medical history of both hypertension and hyperlipidemia. The same subject had DBP above 110 mmHg in each Experimental Session, suggesting that pre-existing cardiovascular risk factors beyond hypertension itself may be associated with further elevations in blood pressure, though a larger sample would be needed to establish this. None of the participants with controlled hypertension experienced AEs of the cardiovascular system and no lasting effects on the transient increases in BP measurements have been observed in any of the clinical trials.

After any MDMA dose, heart rate above 110 bpm was detected in 38% of participants with PTSD, 33.3% of participants on the autism spectrum with social anxiety, and 37.5% of participants with anxiety associated with life-threatening illness. Both highest peak and maximum duration above 110 bpm were observed in 125 mg MDMA-assisted sessions. A comparison of participants receiving the supplemental dose to those who only received the initial dose in MP-1 indicate that the supplemental dose did not cause further elevation in blood pressure and heart rate beyond the initial dose.

7.3.4 Immunological Effects

Humans exhibit transient immunological changes after a dose of 100 mg, including reduced numbers of CD4 cells, increased numbers of NK cells, and an increase in levels of immunosuppressive and anti-inflammatory cytokines compared with levels of pro-inflammatory and immunostimulating cytokines. In several respects, these effects are similar to those that occur with other psychoactive substances, so are not unique to MDMA. Immunological effects last for approximately 24 hours after administration, and most arise indirectly from serotonin release. The significance of these immunological effects remains unclear. Based on results from trials conducted by the sponsor to date, the impact of these effects is expected to be modest and will be further evaluated in the ongoing Phase 3 clinical program.

7.3.5 Hepatic Effects and Other Laboratory Values

Phase 1 studies conducted outside of sponsor support involving administration of MDMA to healthy volunteers have not reported any results of liver function after MDMA administration, and a recent published examination of safety data in a pooled sample of healthy participants found no changes in hepatic function assessed via standard liver panel. There have been no reported adverse effects on the liver from these studies. The first two sponsor-supported Phase 2 studies (MP-1, MP-2) assessed liver function after completion of two or three blinded Experimental Sessions. No clinically or statistically

significant changes in liver function occurred in MP-1. Values for laboratory tests were within the normal range in MP-1. No AEs related to liver function have been reported in subsequent sponsor-supported studies. Only one participant in the MP-2 study reported a clinically significant hepatic abnormalities, likely due to hereditary factors. The other observed laboratory value (increased ESR) indicated inflammation in a subject with a medical history of breast cancer 3 months after the last administration of MDMA as an AE unrelated to the Investigational Product.

7.4 Risk Assessment and Mitigation

Study procedures and eligibility criteria have been developed based on Phase 2 PTSD trials to exclude potential participants with pre-existing exclusionary medical conditions that would exacerbate risk. The therapy teams and site physicians are available via mobile phone throughout the study if any problem occurs when a participant is not at the site. In the event of a medical emergency or any other medical problem during an Experimental Session, the site physician will be immediately available by telephone, and based on assessment of the situation, they will make the decision to either evaluate the participant themselves at the site, or arrange for transfer of the participant to the Emergency Department.

Risk mitigation procedures are described by risk category below. Risk Categories were determined by review of possible risks within the Risk Assessment and Categorization Tool (RACT).

7.4.1 High Level Risks

High Risk does not indicate an event is more likely to happen but indicates per the Risk Assessment Categorization Tool (RACT) assessment that new and or more complex procedures are required in the study to ensure screening is adequate to eliminate or manage the risk in the patient population. No high-level risks of MDMA have been identified based on the RACT assessment.

7.4.2 Medium Level Risks

Medium Risk does not indicate the likelihood the event will occur but indicates per the RACT assessment that new or many procedures, which are not complex, are needed to ensure screening is adequate to eliminate or manage the risk in the patient population.

Cardiovascular and Cerebrovascular Risks and Mitigation

MDMA is known to transiently increase heart rate and blood pressure in a dose-dependent manner that is generally not problematic for physically healthy individuals. These changes should last no more than 8 hours. Participants with PTSD in MAPS-sponsored Phase 2 studies do not appear to differ from healthy individuals in this sympathomimetic, physiological response. Most people do not experience elevations in cardiovascular parameters that exceed those seen after moderate exercise. An examination of safety data drawn from Phase 2 studies of MDMA-assisted psychotherapy

detected a dose-dependent increase in SBP but not DBP. Characterization of sympathomimetic effects among participants with controlled hypertension is ongoing.

Risks posed by elevated blood pressure will be addressed by excluding people with pre-existing uncontrolled hypertension and monitoring blood pressure and pulse, as described in study protocols. Before and after drug administration in Experimental Sessions, the therapy teams monitor vital signs. The therapy teams attend to clinical signs and symptoms during Experimental Sessions, such as chest pain, shortness of breath, neurological deficit or confusion other potential indicators of end organ effects of hypertension that prompt additional vital sign measurements and intervene if appropriate. Therapy teams notify the site physician if this occurs for evaluation. If any participant has neurological deficits, as assessed by the site physician, whether they are associated with hypertensive crisis, they will be monitored as described above, for rare complications of cardiovascular effects, such as stroke or acute myocardial infarction (AMI). If a participant experiences ischemic type chest pain, whether it is associated with hypertensive crisis, the study physician will be contacted immediately, and the participant will be taken to an emergency room by ambulance as expeditiously as possible to assess the patient and act in accordance with the assessment of the expert on site supported by national and local/ AHA and ESC Guidelines. Pending transport to the hospital the site team may take any measures ordered by the site physician including administering medication such as aspirin or nitroglycerin or providing supplemental oxygen per local standards. If further evaluation at the hospital reveals that the participant has had an AMI, they will be well within the time frame required for definitive therapy. If evaluation at the hospital reveals an acute ischemic stroke, there will be enough time to administer recombinant tissue plasminogen within the 3-hour time frame recommended in the 2019 American Heart Association/American Stroke Association Academy of Neurology guideline [677].

As the characterization of QT effects for the Active Pharmaceutical Ingredient (API) is ongoing, QT interval may be evaluated in the event of hospitalization for management of cardiovascular or cerebrovascular event. If at any time a participant develops a QT/QTc interval >450 ms or of >30 ms over baseline during ECG evaluation, the participant will be discontinued from treatment.

Psychological Risks and Mitigation

Mild anxiety and depressed mood are occasionally reported 1 to 3 days after MDMA administration [20, 21]. Psychological distress from MDMA could arise from the first indications of MDMA effects until the last effects have dissipated or even later. Anxiety or distress during the session may last for as little as 5 minutes or for as long as 5 hours or more. In addition, psychological distress could arise following an Experimental Session as a result of participants having difficulty integrating their experience after the MDMA effect has subsided. In previous Phase 1 and Phase 2 studies, these symptoms have been self-limiting and have responded well to reassurance from the therapy team, with occasional use of benzodiazepines for anxiety. In this study, participants will have the intention of confronting and working through traumatic experiences. Accordingly, signs of psychological distress, panic, or other unpleasant psychological reactions are to be expected and may be considered an element of the psychotherapeutic process.

Proper preparation and follow-up support will reduce the difficulties participants might have with acute or sub-acute reactions. The potential for destabilizing psychological distress will be minimized by:

- Excluding people who might be more vulnerable to it (such as people diagnosed with bipolar affective disorder type 1 or with psychotic disorders).
- Preparatory Sessions of non-drug psychotherapy before the Experimental Session.
- Creating an atmosphere of trust during the Experimental Session.
- Close monitoring.
- Phone contact with participants during the week after the Experimental Session.
- Integrative Sessions.
- Overnight stays at the study site for the night of each Experimental Session for PTSD studies. Qualified personnel will be available during the overnight stay to respond to the needs of the participant. Attendants will be instructed to contact the therapy team upon request or at the appearance of signs of a potential SAE.

During the Preparatory Sessions, participants will be made aware of the fact that difficult emotions, including grief, rage, fear, or panic, may arise during Experimental Sessions. Every effort will be made to help participants resolve difficult symptoms and to arrive at a more comfortable and relaxed state by the conclusion of the Experimental Session, including empathic listening on the part of the therapy team and performance of diaphragmatic breathing by participants.

If the participant is severely agitated, anxious, in danger of self-harm or suicide, or is experiencing any other severe psychological distress, at the end of a psychotherapy session, at least one member of the therapy team remains with the participant for at least 2 more hours. During this time, the therapy team employs affect management techniques, talks with the participant to help them gain cognitive perspective of their experiences, and helps the participant implement the self-soothing and stress inoculation techniques presented during the Preparatory Sessions. If the participant remains severely anxious, agitated, in danger of self-harm or suicide, or is otherwise psychologically unstable at the end of the 2-hour stabilization period, the site physician and therapy team decide between the following options:

1. If severe distress occurs at the end of an Experimental Session, a psychiatric nurse, therapeutic assistant, physician, or therapy team member would stay with the participant until the severe distress resolves or until the time of their Integrative Session appointment the following morning. The therapy team would then meet with the participant daily until the period of destabilization has passed.
2. If the participant experiences severe, persisting emotional distress, such as panic attacks, severe generalized anxiety, or insomnia following an Experimental Session, a licensed therapy team member or the site physician may prescribe a benzodiazepine (specifically, lorazepam) and/or sleep aid (e.g., zolpidem). The site physician should not prescribe an SSRI, SNRI, or monoamine oxidase inhibitor (MAOI) in this context, unless it has been determined that the participant

will be withdrawn from the study. Residual symptoms would be addressed during the frequent follow-up psychotherapy visits with the therapy team.

3. If a participant should become psychotic, arrangements would be made to stabilize them or transfer them to the Emergency Department (ED) if hospitalization is necessary. If any participant is hospitalized after a severe psychological reaction they would be suspended from the protocol until after recovery or stabilization, at which time the investigator and/or site physician would carefully evaluate the participant's emotional status.

For those participants engaged in an ongoing therapeutic relationship with a psychotherapist or psychiatrist, the participant's outside therapist(s) would be involved in the management of any psychiatric complications. For those participants engaged in an ongoing psychotherapeutic relationship with the investigator or member of the therapy team, the management of any psychiatric complications will be undertaken by them in their capacity as the participant's therapist.

7.4.3 Low Level Risks

Low Level Risk does not indicate the likelihood the event will occur but indicates per the RACT assessment that no new or complex procedures are needed to ensure screening is adequate to eliminate or manage the risk in the patient population.

Thermoregulatory Risks and Mitigation

MDMA administered in a controlled setting produces only a slight increase in body temperature [21]. Ambient temperature does not enhance or attenuate this slight elevation in humans. In data gathered from sponsor-supported Phase 2 studies, it was found that compared to placebo, a higher percentage of participants receiving MDMA had peak body temperatures greater than 1°C above baseline. However, there was no strong relationship between dose of MDMA and peak body temperature or between MDMA dose and elevation above threshold of 1°C above baseline.

Ambient temperature should be kept at a comfortable level during Experimental Sessions. If temperature rises more than 1°C or the participant states that they feel hot, attempts should be made to decrease body temperature and increase comfort by removing blankets and layers of clothing, decreasing the ambient temperature, and, if necessary, directing a fan toward the participant. If at any time the temperature rises more than 1.5°C above baseline despite these efforts, the site physician should be consulted for further evaluation and treatment.

Osmoregulatory Risk and Mitigation

MDMA administered in a controlled setting is not expected to have any risks of osmoregulatory changes. Participants are not allowed to drink more than three liters of electrolyte-containing fluids over the course of the Experimental Session and fluid intake is spread out appropriately during the session. If a participant exhibits any signs of toxicity or clinically significant dilutional hyponatremia despite these precautions after an

Experimental Session, they would not receive another Experimental Session unless it is approved by the investigator, site physician, and the Medical Monitor.

Genotoxicity Risk and Mitigation

To reduce the risk of metabolic activation and formation of nitroso-derivatives of MDMA due to interactions with nitrates or nitrites in food, participants are required to have fasted (no intake other than alcohol-free liquids) for 10 hours prior to drug administration in Experimental Sessions.

Reproductive and Developmental Risks and Mitigation

Risks posed by MDMA to pregnant people are not known. One of two studies of Ecstasy users suggest that use of Ecstasy and other drugs during pregnancy may be associated with some abnormalities at birth while the other failed to find this association [631, 632].

Pregnant and lactating people will be excluded from participation in the study. Participants who are able to become pregnant must have a negative pregnancy screen before undergoing each Experimental Session and must agree to use adequate birth control for the duration of the study during the Treatment Period. Procedures have been put in place to mitigate risk of reproductive or developmental exposure to MDMA.

7.4.4 Minimal Risks

Minimum Level Risk does not indicate the likelihood the event will occur but indicates per the RACT assessment that no procedures are needed beyond basic monitoring to ensure screening is adequate to eliminate or manage the risk in the patient population.

Common Expected AEs

Common expected AEs were typically observed during Experimental Sessions but were transient and diminished as MDMA was metabolized and excreted over the next 72 hours after dosing. Anxiety and fatigue were the most frequently reported reactions during Experimental Sessions for both active dose MDMA and inactive placebo. In the blinded and open-label active MDMA dose groups, participants most frequently reported muscle tightness and nausea. The only SAEs that were reported by more than one participant were depressed mood and panic attack, which occurred in the blinded 75 to 125 mg MDMA group. AEs were typically self-limiting. Anxiety and poor sleep respond to management with short-acting low dose benzodiazepines (specifically, lorazepam) or sleep aids as needed per clinical judgment of the site physician.

Potential Neurotoxicity Associated with Ecstasy Use

Some researchers believe that MDMA is neurotoxic in humans even at doses used in clinical trials [678]. However, these claims are based on studies that employed inappropriately high doses of MDMA utilized in animal studies and on human studies comparing the effects of repeated use of Ecstasy, often along with other drugs. Meanwhile, another recently published meta-analysis has taken careful steps to overcome

methodological limitations in previous work and found only modest evidence of neurotoxicity [80]. The sponsor has carefully considered the risks of such neurotoxicity and concludes that they are minimal in the proposed study. This conclusion is supported by empirical and toxicokinetic evidence and is consistent with the lack of toxicity reported in previous clinical MDMA studies. It does not appear that MDMA-assisted psychotherapy negatively impacts cognitive function.

Abuse Potential

Despite its classification as a Schedule I drug, an examination of findings in humans and animals suggests that MDMA possesses moderate abuse potential that is higher than that reported for "classic hallucinogens" like psilocybin, but lower than that reported for psychostimulants, such as cocaine or methamphetamine. Studies assessing prevalence of problematic Ecstasy use or dependence suggest that a small percentage of individuals, especially those with prior psychological difficulties, may develop problematic Ecstasy use or dependence. Across MAPS-sponsored early Phase 2 studies of MDMA-assisted psychotherapy for people with PTSD, 8 of 92 participants reported using Ecstasy subsequent to study participation, with 6 of the 8 participants having used Ecstasy prior to study enrollment. Several participants volunteered that they would not seek out Ecstasy outside of a psychotherapeutic setting. Diversion is not an issue for sponsor-supported studies because MDMA will only be administered under the supervision of the clinical investigator and no take-home doses are permitted. MDMA is handled following all regulations pertaining to the handling and dispensing of controlled substances within research studies.

7.5 Reference Safety Information for Regulatory Reporting

The theoretical risks based on case reports of mortality and morbidity in the published scientific literature on MDMA or Ecstasy are presented in Table 28 below. All SARs at least possibly related to MDMA and included in Table 28 will be considered expected and reported as Suspected Adverse Reactions (SARs), while those not included in Table 28 will be considered unexpected and are subject to expedited reporting as Suspected Unexpected Serious Adverse Reactions (SUSARs) in the U.S. Only one SAR, an increase in ventricular extrasystoles, has been observed in the Clinical Development Program of MDMA-assisted psychotherapy.

Table 28: Reference Safety Information Based on Case Reports of Morbidity and Mortality Possibly Associated with MDMA

Body System	Adverse Reaction
Thermoregulatory Disorders (MedDRA "Body Temperature conditions" under "General Disorders and Administrative Site Conditions"	Hyperthermia, Hyperpyrexia, (leading to: Rhabdomyolysis, Hypoglycemia)
Cardiac Disorders	Cardiac valve disease (Valvular Heart Disease), Ventricular fibrillation, Cardiac arrest, Arrhythmia, Dysrhythmia, Myocardial infarction, Generalized tonic-clonic seizure, Acute coronary syndrome, Myocardial necrosis, Cardio-respiratory arrest, Cardiomyopathy

Osmoregulatory Disorders (MedDRA 17.1 "Electrolyte and fluid balance conditions" under "Metabolism and Nutrition Disorders	Syndrome of Inappropriate Antidiuretic Hormone, Urinary retention, Hyponatremia, (sequelae: Cerebral oedema, Acute renal failure
Hepatobiliary Disorders	Acute fulminant hepatitis, Liver disease, Disseminated intravascular coagulation
Injuries, Poisonings, and Procedural Complications	Anaphylactic shock, Facial rash eruption, swollen lip (allergic or mechanical injury)
Nervous System Disorders	Cerebral oedema; Hemorrhage, Infarct, Hippocampal sclerosis, Encephalopathy, Amnestic syndrome
Dental And Gingival Disorders (under "Gastrointestinal Disorders")	Xerostomia, Bruxism, Dental erosion
Psychiatric Disorders	Psychotic episode, Depressive episode
Respiratory, Thoracic, and Mediastinal Disorders	Subcutaneous Pneumomediastinum, Epidural pneumatosis, Diffuse alveolar hemorrhage, Asthma
Eye Disorders	Lagophthalmos, Keratopathy, Bilateral sixth nerve palsy

The Reference Safety Information (RSI) below outlines expected Serious Adverse Reactions (SARs) for regulatory reporting purposes in the European Economic Area (EEA) region and the information within the RSI does not present a comprehensive overview of the safety profile of the IMP (Table 29).

Table 29: Serious Adverse Reactions for the IMP Considered Expected for Safety Reporting Purposes in EEA Region

System Organ Class	SARs	As of May 31, 2019: Number of subjects exposed within the development program (N)=267 Number of subjects exposed outside the development program (N)=1570		
		All SARs	Occurrence of fatal SARs	Occurrence of life-threatening SARs
		N* (%)	N (%)	N (%)
None	None	0 (0.0)	0 (0.0)	0 (0.0)

* N=number of subjects who have experienced the SAR

In the EEA region, no SARs are considered expected by the sponsor for the purpose of expedited reporting of SUSARs and identification of SUSARs in the "Cumulative summary tabulation of serious adverse reactions" in the Development Safety Update Report (DSUR) for the IMP. Although one SAR has been observed to date in MAPS-sponsored clinical trials, it has not been observed more than once and hence does not meet the definition of an SAR for the RSI.

8.0 Conclusions

Based on the current state of scientific knowledge, the risk for subjects meeting criteria for clinical studies who are exposed to MDMA at the single-dosing schedule, administered up to 3 times per treatment course, used in sponsor-supported studies appears to be low. The overall rates of AEs and reactions across phase 2 studies are low and the reactions and AEs are mostly transient and self-limiting. Many of the AEs and

expected reactions reported in the studies are likely related to background events representing the underlying illness being treated, or the expected result of psychotherapy addressing traumatic experiences.

Future studies conducted by the sponsor are intended to further develop the safety profile of MDMA in the PTSD subject population, and subjects with other indications. The sponsor is exploring the use of MDMA-assisted psychotherapy in the treatment of anxiety, including social anxiety in people on the autistic spectrum and anxiety resulting from a life-threatening illness. MDMA-assisted psychotherapy appears to be a promising treatment method for chronic PTSD. More clinical trials in larger subject populations are warranted. It is hoped that MDMA, with its unique pharmacological mechanisms combined with a novel mode of administration in conjunction with psychotherapy, can improve upon first line PTSD and anxiety treatments in terms of side effect profiles, efficacy and duration of effect. Overall, the benefit/risk ratio of MDMA-assisted psychotherapy appears to be favorable for the continuation of the development of this modality in the treatment of PTSD, an indication with a high unmet medical need.

Appendix

Appendix Table 1: Summary of Investigator-Initiated Trials with MDMA

Funding/grants/ support	Study design	Sample given MDMA[A]	Demographics	Dose of MDMA	Comparator	Safety findings
ACTRN12613000685718 (Australia/New Zealand trial registry, 2013)	Two studies; Randomized, double-blind placebo controlled, within-subjects design	13	Study 1: 3/2 (M/F) Average age 60 Study 2: 6/2 (M/F) Average age 53.4	Study 1: 30 mg (~0.42 mg/kg) Study 2: 70 mg (~1 mg/kg)	Placebo	No AEs of concern reported, no interventions required. No SAEs reported [679]
NCT03019822	Randomized, double-blind, placebo-controlled, cross-over design. Four Experimental Sessions.	28	14/14 (M/F) Age range 25-45	125 mg (~1.8 mg/kg)	Placebo, 100 µg LSD, 40 mg d-amphetamine	No AEs of concern were reported, and no interventions required. No SAEs reported. [584]
NCT04158778	Open-label MDMA, two sessions	7	3/1 (M/F), 3 not specified Age range 34-64	125 mg (~1.8 mg/kg)	None	No AEs of concern, no interventions required. No SAEs reported. [680]
DA02812; 2T32GM007281	Double-blind, randomized, placebo-controlled within-subjects crossover (4 sessions)	36	18/18 (M/F) Average age 24.8; 22 Caucasian, 5 African-American, 5 Asian, 4 Other	0.75 mg/kg 1.5 mg/kg	Placebo, 20 mg methamphetamine	No AEs of concern were reported, and no interventions required. No SAES were reported. [681, 682]
Excellence Aware, Medical Research Council Fellowship Grant MR/J008915/1 Research Council [IoPPN-MRC] Excellence award	Double-blind, placebo-controlled crossover study	20	20/0 (M/F) Average age 24.8	100 mg (~1.4 mg/kg)	Placebo	No AEs of concern, no interventions required. No SAEs reported. [610, 683]
Beckley Foundation Channel 4	Double-blind, placebo- controlled	25	18/7 (M/F) Average age 34	100 mg (~1.4 mg/kg)	Placebo (Ascorbic acid)	No AEs of concern, no interventions required. No SAEs reported [32, 598, 603, 684, 685]

Funding/grants/ support	Study design	Sample given MDMA[A]	Demographics	Dose of MDMA	Comparator	Safety findings
	crossover with repeated measures *Five participants recorded for documentary without any further analysis					
NCT01951508	Randomized, double-blind, placebo-controlled crossover design, 5 conditions	24	12/12 (M/F) Age range 19-29	125 mg (~1.8 mg/kg)	Placebo, 60 mg methylphenidate, 600 mg modafinil	No AEs of concern were reported, and no interventions required. No SAEs reported. [611, 686, 687]
NCT01771874	Randomized, double-blind, placebo-controlled, crossover design. 4 conditions. Drug interaction study	16	8/8 (M/F) Average age 24.3	125 mg (~1.8 mg/kg)	Placebo, bupropion (300 mg 1 week prior) pretreatment	Bupropion did not alter adverse effects of MDMA No AEs of concern were reported, no intervention required. No SAEs reported. [556, 565, 574, 592]
NCT01465685	Randomized, double-blind, placebo-controlled, crossover design. 4 conditions. Drug interaction study	16	8/8 (M/F) Average age 24.8	125 mg MDMA (~1.8 mg/kg)	Placebo (mannitol), 60 mg methylphenidate pretreatment	Concomitant methylphenidate does not enhance the risk of MDMA-induced increase in body temperature. No AEs of concern reported, and no interventions needed. No SAEs reported. [541, 595, 688]
NCT01386177	Randomized, placebo-controlled double-blind crossover design, four conditions	16	8/8 (M/F) Average age 25.8	125 mg (~1.8 mg/kg)	Placebo, doxazosin	No AEs of concern were reported, and no interventions required. No SAEs reported. [664]
NCT01616407	Randomized, double-blind, placebo-controlled, crossover design. 3 conditions.	30	15/15 (M/F) Age range 18-32	75 mg (~1.1 mg/kg)	Placebo, methylphenidate pretreatment	No AEs of concern were reported, and no interventions required. No SAEs reported. [587]

Funding/grants/ support	Study design	Sample given MDMA[A]	Demographics	Dose of MDMA	Comparator	Safety findings
NCT00990067	Randomized, double-blind, placebo-controlled, crossover design. 4 conditions.	16	8/8 (M/F) Average age 26.1	125 mg (~1.8 mg/kg)	Placebo, duloxetine pretreatment	No AEs of concern were reported, and no interventions required. No SAEs reported. [224, 583]
NCT01270672	Randomized, placebo-controlled double-blind crossover design, four conditions	16	8/8 (M/F) Average age 24.2	125 mg (~1.8 mg/kg)	Placebo, 50 mg carvedilol pretreatment	No AEs of concern were reported, and no interventions required. No SAEs reported. [223]
NCT00886886	Randomized, double-blind, placebo-controlled, crossover design. 4 conditions.	16	8/8 (M/F) Average age 25.7	125 mg (~1.8 mg/kg)	Placebo, reboxetine pretreatment	No AEs of concern reported, no intervention required. No SAEs reported. [582]
European Union grant TREN-05-FP6TR-S07.61320-518404-DRU	Double-blind, placebo-controlled within-subjects (four conditions)	16	8/8 (M/F) Average age 22.0	25 mg (~0.36 mg/kg), 50 mg (~0.7 mg/kg) or 100 mg (~1.4 mg/kg)	Placebo	Sleep deprivation worsened driving skills (signs of weaving); no dose of MDMA mitigated, or worsened, performance. No AEs of concern were reported, and no interventions required. No SAEs reported. [604, 620, 689]
European Comission Grant GMAI-2000-27043	Double blind, placebo controlled, 3-way crossover (within-subjects), treatment-balanced	18	9/9 (M/F) Average age 26.22	75 mg (~1.1 mg/kg)	Placebo, 20 mg methylphenidate	No AEs of concern were reported, and no interventions were required. No SAEs were reported. [621, 624, 625]
IMMORTAL research consortium funded by EU grant GMA1-2000-27043.	double blind, placebo-controlled, 6-way crossover	18	9/9 (M/F) Average age 26.6	75 mg (~1.1 mg/kg), 100 mg (~1.4 mg/kg)	Placebo, ethanol	No AEs of concern were reported, and no interventions were required. No SAEs were reported. [622, 623]
No grants listed, internal funds	double-blind, placebo controlled, within subjects, two-way,	14	7/7 (M/F) Average age 22.9	50 mg (~0.7 mg/kg) followed 3 h later by 75 mg (~1.1 mg/kg)	Placebo	No AEs of concern reported, and no interventions required. No SAEs reported. [690, 691]

Funding/grants/ support	Study design	Sample given MDMA[A]	Demographics	Dose of MDMA	Comparator	Safety findings
Financial support for this study was provided by the Dutch Ministry of Transport.	Double-blind, placebo-controlled three-way cross-over (within-subjects)	12	8/4 (M/F) Average age 23.5	75 mg (~1.1 mg/kg)	Placebo, crossed with placebo or ethanol	No AEs of concern reported, and no interventions required. No SAEs reported. [618]
NTR 1416	double-blind, randomized, placebo controlled, (within-subjects) crossover	14	11/3 (M/F) Average age 23.43		Placebo	No AEs of concern reported, and no interventions required. No SAEs reported. [601, 602]
NTR 2352; Netherlands Organization for Scientific Research (NWO) Grant number: 400-05-096; DIUE de la Generalitat de Catalunya (2009 SGR 718	double-blind, placebo controlled, within-subject	15	11/4 (M/F) Age range 20-28, Average age 22.2	75 mg (~1.1 mg/kg)	Placebo, 20 mg memantine	No AEs of concern reported, and no interventions required. No SAEs reported. [692]
NTR 3691; NWO Grant: 400-07-2013; DIUE Grant: 2014SGR 680	Double-blind, placebo-controlled within subjects 2x2 crossover	20	12/8 (M/F) Average age 21.2		Placebo, 40 mg ketanserin	No AEs of concern reported, and no interventions required. No SAEs reported. [693]
NTR 1421	Placebo controlled, within subject	17	11/6 (M/F) Average age 21.0	75 mg (~1.1 mg/kg)	Placebo, crossed with placebo or 750 mg metyrapone	No AEs of concern reported, and no interventions required. No SAEs reported. [594]
NTR 2636; NWO Grant 400-07-2013	2×2 double blind, placebo controlled, within-subject	20	12/8 (M/F) Age range 18-26	75 mg (~1.1 mg/kg)	Placebo, crossed with 20 mg pindolol, intranasal oxytocin (40 IU+16 IU)	No AEs of concern reported, and no interventions required. No SAEs reported. [591]

Funding/grants/ support	Study design	Sample given MDMA[A]	Demographics	Dose of MDMA	Comparator	Safety findings
NTR 3691; NWO Grant: 400-07-2013; DIUE Grant: 2014SGR 680	2×2 double blind, placebo controlled, within-subject	20	12/8 (M/F) Average age 21.2	75 mg (~1.1 mg/kg)	Placebo, crossed with placebo or 40 mg ketanserin	No AEs of concern were reported, and no interventions required. No SAEs reported. [609]
NWO grant 400-05-096; NTR 2352	double blind, placebo controlled, within-subject, 6 conditions	17	9/8 (M/F) Average age 22.76	75 mg (~1.1 mg/kg)	Placebo, 20 mg pindolol, 50 mg ketanserin	No AEs of concern were reported, and no interventions required. No SAEs reported. [86, 186]
NTR 3691	Randomized, double-blind, placebo controlled	18	9/9 (M/F) Average age 21.4; 5-HTTLPR genotype: 5 (l/l), 13 (*/s)	75 mg (~1.1 mg/kg)	Placebo	No AEs of concern, and no interventions needed. No SAEs reported. [293]
DA02812	4-session, within-subject, double-blind, placebo controlled, four conditions	21	10/9 (M/F), 2 not specified; Average age 24.4; 17 Caucasian, 2 Asian, 1 African-American, 1 of mixed race	0.75 mg/kg; 1.5 mg/kg	Placebo, 20 mg methamphetamine	No AEs of concern were reported, and no interventions required. No SAEs reported. [33, 82]
National Institutes of Health (NIH) (DA017716 and DA016776) and the NIH/National Center for Research Resources (UCSF-CTSI UL1 RR024131)	Within-subject double-blind, placebo controlled	12	6/6 (M/F) Average age 24	1.5 mg/kg	Placebo	No AEs of concern reported, no interventions required. No SAEs reported. [694]
DA02812	Double-blind, randomized 3-session; ascending dose, randomized placebo	9	7/2 (M/F): Average age 24.0; 6 Caucasian	0.75 mg/kg; 1.5 mg/kg	Placebo (lactose)	No AEs of concern were reported, and no interventions required. No SAEs reported. [41]

Funding/grants/ support	Study design	Sample given MDMA[A]	Demographics	Dose of MDMA	Comparator	Safety findings
R01 DA002812; T32 DA007255	3-session, counter-balanced, double-blind design	36	18/18 (M/F): Average age 24.6; 23 Caucasian	0.75 mg/kg; 1.5 mg/kg	Placebo (D-glucose)	No AEs of concern were reported, and no interventions required. No SAEs reported. [614, 626] Sponsor conducted post-hoc analysis of 2-lead ECG and found low likelihood of QT prolongation
R01 DA02812 and R21 DA026579	4-session, mixed within-and-between-subject, double-dummy design	14	12/2 (M/F) Average age 25.4	0.75 mg/kg; 1.5 mg/kg	Placebo (lactose), 20 or 40 IU intranasal oxytocin	No AEs of concern were reported, and no interventions required. No SAEs reported. [589, 695]
DA02812; DA026570	4-session, mixed within-and-between-subject, double-dummy design	65	40/25 (M/F) Average age 23.8	0.75 mg/kg; 1.5 mg/kg	Placebo (lactose), 20 or 40 IU intranasal oxytocin	No AEs of concern were reported, and no interventions required. No SAEs reported. [56, 616, 696]
R21 DA026570 and R01 DA02812	3-session, mixed between- and within-subject; 3 conditions: solitary, in the presence of a research assistant, or in the presence of two other active participants receiving the same dose (MDMA or placebo)	33	24/9 (M/F) Average age 25; 22 Caucasian, 6 African, 4 Hispanic, 1 Asian	0.5 mg/kg; 1.0 mg/kg (max to 125 mg)	Placebo, between group compared environment (alone, with sober researcher vs. with participant on same drug)	No AEs of concern were reported, and no interventions required. No SAEs reported. [612]
Supported by the National Institutes of Health (NIH) (DA017716 and DA016776) and the NIH/National Center for Research Resources (UCSF-	Within-subject double-blind, placebo controlled	12	6/6 (M/F) Average age 24	1.5 mg/kg	Placebo	No AEs of concern were reported, no interventions required. No SAEs reported. [694]

Funding/grants/ support	Study design	Sample given MDMA[A]	Demographics	Dose of MDMA	Comparator	Safety findings
CTSI UL1 RR024131)						
DA02812; T32 MH020065; T32 GM007281	Mixed; Double-blind within-subject (stress condition) and between-subject (treatment) design	26	20/6 (M/F) Average age 24.6; 10 Caucasian, 2 African American, 5 Asian, 9 Other	0.5 mg/kg; 1.0 mg/kg	Placebo (lactose), stress (Trier Stress Test) and no-stress sessions	No AEs of concern were reported, and no interventions required. No SAEs were reported. [597]
DA031796; DA02812	2-session, between-subject, randomized, placebo-controlled, double-blind	40	Group 1: 10/10 (M/F) Average age 24.9; 55% Caucasian, 5% Black, 25% Asian, 15% Other; Group 2: 10/10 (M/F) Average age 22.4; 55% Caucasian, 5% Black, 15% Asian, 25% Other	1.0 mg/kg	Placebo (dextrose)	No AEs of concern reported, and no interventions required. No SAEs reported. [697]
R01 DA002812; T32 DA007255	Double-blind, 3-session, within-subjects, counter-balanced	36	18/18 (M/F) Average age 24.6; 24 Caucasian, 4 African-American, 1 Asian, 7 Mixed Race	0.75 mg/kg; 1.5 mg/kg	Placebo (lactose)	MDMA increased desire to take drug again over placebo control. No interventions were needed. No SAEs occurred. [35]
Funding from MAPS [not part of IND]	Double blind ascending dose and randomized and placebo controlled within each dose condition; discontinued prematurely due to	4	0/6 (M/F) Age range 29-49; no history of MDMA use, PTSD from sexual assault.	50 mg, 75 mg	Placebo (2 of 6 received placebo only)	No AEs of concern reported, and no interventions required. No SAEs reported. [81]

Funding/grants/ support	Study design	Sample given MDMA[A]	Demographics	Dose of MDMA	Comparator	Safety findings
	political/institutional conflicts					
NCT02232789	Randomized, double-blind, crossover, and placebo-controlled	12	12/0 (M/F) Average age 31 years	100 mg (~1.4 mg/kg)	Placebo, 200 mg mephedrone	No AEs of concern reported and no intervention required. No SAEs reported.[698]
2001SGR00407, 2005SGR00032, 2009SGR718, FIS 98/0181 and 01/1336	Randomized, double-blind, crossover, and placebo-controlled, two sessions	10	10/0 (M/F) Average age 24.9	100 mg (~1.4 mg/kg), 50 mg+100 mg 2 h later	Placebo	No AEs of concern reported, and no interventions required. No SAEs reported. [260]
NIDA grant 5R01BA017987-01, DIUE (2009 SGR 718), grant (FIS-RTA RD06/0001/1009), and (MICINN FI09/00355), ISCIII-FIS-CAIBER CAI08/01/0024. fellowship Rio Hortega (FIS CM08/00051).	Open-label, single-dose pharmacokinetic study,	27	15/12 (M/F), Age not specified, recreational users of Ecstasy	1.4 mg/kg (75-100 mg)	N/A	No AEs of concern reported, and no interventions required. No SAEs reported. [570]
NIDA 5R01BA0-17987-01, MICINN 510900355, FISTRA grant, others; NCT01447472 R01BA017987-01), MICINN FI09/00355), grant no. RD06/0001/0026),	Open-label, two-session within-subjects design Open label within-subjects design, two sessions	21	12/9 (M/F) Average age 26.3; Caucasian.	1.5 mg/kg MDMA (75-100 mg)	caffeine vs MDMA + caffeine administered 4 h post-MDMA DXM, vs MDMA + DXM administered 4 h laster	No AEs of concern were reported, nor interventions required. No SAEs were reported. [553]

Funding/grants/ support	Study design	Sample given MDMA[A]	Demographics	Dose of MDMA	Comparator	Safety findings
AGAUR; grant no. 2009 SGR 718).NIDA 5R01BA0-17987-01, MICINN 510900355, FISTRA grant, others; NCT01447472						
Grants FIS 97/1198, FIS 98/0181, FIS 00/0777, and FIS 01/1336 from Fondo de Investigacio´n Sanitaria, Madrid, Spain; Grant 2001SGR00407	Randomized, double-blind, placebo-controlled crossover Drug interaction study	12	12/0 (M/F) Age not specified	100 mg (~1.4 mg/kg)	Placebo; with and w/out 3 prior days of 20 mg paroxetine	No AEs of concern, and no interventions needed. No SAEs reported. [552]
Generalitat de Catalunya (2001SGR00407), Fondo de Investigacíon Sanitaria (98/0181 and 01/1336)	Randomised, double-blind, cross-over, placebo controlled	10	10/0 (M/F) Age range 21-33; previous experience with psychostimulants, cannabis, or hallucinogens	100 mg day 1+100 mg day 2 (~1.4 mg/kg per day)	Placebo	Diagnostic criteria of isolated systolic hypertension (>140 mmHg) were met by 6 subjects following the first dose of MDMA and 8 subjects following the second dose; mean duration of 1 h (range 0.5-2) following the first dose and 1.4 h (range 0.5-3) following the second dose. Two subjects met diagnostic criteria of sinus tachycardia (>100 beats/minute), both following the second dose of MDMA. Tachycardia lasted between 15 and 30 minutes. No intervention required and no SAEs reported. [559]
FIS 98/0181, CIRIT 99-SGR-00242, and PNSD	Open label within-subjects/time course study	27	27/0 (M/F) Age not specified	100 mg (~1.4 mg/kg), second dose 100 mg MDMA Second dose of MDMA administered	None	MDMA produced time-dependent decrease in CD4/CD8 T-cell ratio due to a decrease in the number of CD4 T-helper cells, decrease in functional

Funding/grants/ support	Study design	Sample given MDMA[A]	Demographics	Dose of MDMA	Comparator	Safety findings
				4 hours vs. 24 hours post first dose		responsiveness of lymphocytes to mitogenic stimulation, and a simultaneous increase in natural killer cells. Second dose either 4 or 24 hours later accentuated the findings. No SAEs were reported. [596, 630]
Supported in part by grants from Generalitat de Catalunya (2001SGR00407), Fondo de Investigacíon Sanitaria (98/0181 and 01/1336).	Randomised, double-blind, cross-over, placebo-controlled trial	10	10/0 (M/F), Age range 21-33; previous experience with psychostimulants, cannabis, or hallucinogens	100 mg day 1+100 mg day 2 (~1.4 mg/kg per day)	Placebo	No AEs of concern were reported, and no interventions were required. No SAEs were reported. [699]
FIS 97/1198, CIRIT 1997-SGR-0077, and Plan Nacional sobre Drogas	double blind, double dummy, randomized crossover, placebo-controlled. 4x4 Latin square. States in paper data presented elsewhere in Pacifici et al. 2001	9	9/0 (M/F) Average age 23	100 mg (~1.4 mg/kg) MDMA + ethanol (0.8 g/kg)	Placebo, ethanol alone (0.8 g/kg)	No AEs of concern, and no interventions required. No SAEs reported. [629, 700]
FIS 97/1198, CIRIT (1997SGR00077), ISCIII 97/4344 and Plan Nacional sobre Drogas.	preliminary phase; study phase: double-blind, randomized, crossover and placebo-controlled	14	14/0 (M/F) Average age 26.5	50 mg (~0.7 mg/kg) 75 mg (~1.1 mg/kg) 125 mg (~1.8 mg/kg) 150 mg (~2.1 mg/kg)	Placebo, 40 mg racemic amphetamine	No AEs of concern reported, and no interventions required. No SAEs reported. [18, 19, 24]

Funding/grants/ support	Study design	Sample given MDMA[A]	Demographics	Dose of MDMA	Comparator	Safety findings
R01 DA017987, 2005SGR00032, (FIS-RTA RD06/0001/1009	Controlled open-label drug interaction study (MDMA with dextromethorphan)	15	15/0 (M/F) Average age 26; Age range 19-33	1.5 mg/kg (followed by dextromethor-phan)	N/A	No AEs of concern reported, and no interventions required. No SAEs reported. [551]
5 K08 DA00370/DA/NIDA	Double-blind, placebo-controlled within-subject study	12	6/6 (M/F) Average age 22.3; 10 Caucasian, 1 Asian, 1 Native American	1 mg/kg	Placebo 2 mg/kg d-amphetamine (10 and 20 mg), mCPP (0.5 and 0.75 mg/kg)	No AEs of concern were reported, and no interventions were required. No SAEs were reported. [22]
R01 DA-14874/DA/NIDA	double-blind, 2x2: two sessions at 30 degrees C, two at 18 degrees C, two during MDMA, two during placebo	10	6/4 (M/F) Average age 22.9; 6 White, 3 Black, 1 multiracial	2 mg/kg	Placebo	No AEs of concern were reported, and no interventions were required. No SAEs were reported. [211]
K08 DA00370/DA/NIDA	3 phases (6-session sampling phase, 6-session selection phase, 5-session testing phase), within-subject	8	5/3 (M/F) Average age 25.0; 6 White, 2 Black	1 mg/kg, 1.5 mg/kg	Placebo, 20 mg d-amphetamine, 0.75 mg/kg mCPP	No AEs of concern were reported, and no interventions required. No SAEs were reported. [665]
Joe Young Funds awarded to the Department of Psychiatry and Behavioral Neurosciences by the State of Michigan.	six-group between-group (one group per MDMA and mCPP dose), placebo-controlled, ascending dose order	15	8/14 (M/F) Average age 23.6; 20 Caucasian, 1 bi-racial, one Middle Eastern,	1.1 mg/kg, 1.6 mg/kg, 2.1 mg/kg	Placebo, mCPP (17.5, 35, 52.5 mg/70 kg)	No AEs of concern were reported, and no interventions required. No SAEs were reported. [615]
R01-DA14874	Double-blind, placebo controlled, within-subjects; 3 "sessions" consisting of 3 nights in sleep	7	5/2 (M/F) Average age 25.3; 6 White, 1 Black	2 mg/kg	Placebo, with 8 or 4 hour time in bed	No AEs of concern were reported, and no interventions were required. No SAEs were reported. [579]

Funding/grants/ support	Study design	Sample given MDMA[A]	Demographics	Dose of MDMA	Comparator	Safety findings
	lab [baseline, treatment, recovery night]					
ZonMW 31000062 (Netherlands)	Double-blind, randomized, placebo-controlled crossover (within-subjects); four conditions, crossing MDMA with THC	16	12/4 (M/F) Average age 21.4	100 mg (~1.4 mg/kg)	Placebo; crossed with placebo or THC	One subject reported "feeling unwell" under the influence of MDMA condition. No other AEs of concern reported, and no interventions required. No SAEs were reported. [83, 663, 701, 702]
This research was supported by a grant of ZonMW (31000062)	Double-blind, randomized, placebo-controlled crossover (within-subjects); four conditions	16	9/7 (M/F) Age range 18-29	100 mg (~1.4 mg/kg)	Placebo, crossed with placebo or ethanol	No AEs of concern were reported, and no interventions required. No SAEs were reported. [619, 702-704]
Not listed	Double-blind, crossover, naturalistic study	12	8/4 (M/F) Age range 21-30	75 mg (~1.1 mg/kg)	Placebo, 0.5 g/kg ethanol	No AEs of concern were reported, and no interventions were required. No SAEs were reported. [705]
NIDA (Hart, R01 DA03746)	Double-blind, randomized, placebo-controlled within-subjects	11	9/2 (M/F) Age range 23-39, Average age 29.3	100 mg (~1.4 mg/kg)	Placebo, (20 mg, 40 mg) methamphetamine	No AEs of concern were reported, and no interventions were required. No SAEs were reported. [42, 667]
EU-project DRUID (TREN-05-FP6TR-S07.61320-518404-DRUID).	double blind, placebo controlled, 4 way crossover (MDMA or placebo x ethanol or placebo	19	10/9 (M/F) Age range 21-40, Average age 30.8	100 mg (~1.4 mg/kg)	Placebo, combined with placebo or ethanol	MDMA showed no significant effects on driving compared with placebo. No AEs of concern were reported, and no interventions were required. No SAEs were reported. [706]
Australian Research Council Grant DP0772762	Double-blind, placebo-controlled counterbalanced within-subjects design	61	28/33 (M/F) Average age 25.4	100 mg (~1.4 mg/kg)	Placebo, 0.42 mg/kg methamphetamine	Driving under the influence of MDMA was worse than after both methamphetamine and placebo. No AEs of concern were reported, and no interventions were required. No SAEs were reported. [707-709]

Funding/grants/ support	Study design	Sample given MDMA[A]	Demographics	Dose of MDMA	Comparator	Safety findings
This research was supported by National Institutes of Health DA017716 and DA016776 and the NIH/National Center for Research Resources UCSF-CTSI UL1 RR024131	Study 1: Randomized, placebo-controlled, double-blind within-subjects study w/ 4 conditions Study 2: Randomized, placebo-controlled, double-blind within-subjects study w/ 2 conditions	28	Study 1: 8/8 (M/F) Average age 26.6 Study 2: 6/6 (M/F) Average age 28.6	Study 1: 1.5 mg/kg MDMA, with / without prazosin Study 2: 1.5 mg/kg, followed 30 minutes by 20 ml/kg water	Study 1: Placebo, prazosin pretreatment Study 2: Placebo	Study 1: No AEs of concern reported, no intervention required. No SAEs reported. Study 2: MDMA acutely exaggerates the hyponatremic effects of water. No AEs of concern reported and no interventions required. No SAEs reported. [45, 608]
This research was funded by the Intramural Research Program, National Institute on Drug Abuse, NIH. No grant numbers or NCT number listed	Double-blind, placebo-controlled, randomized within-subjects randomized, counterbalanced, and double-blind design Double-blind, placebo-controlled, randomized within-subjects design	50	33/17 (M/F) Age range 18-35; 73% African-American, 23% Caucasian and 4% unknown/mixed	1.0 mg/kg, 1.6 mg/kg (maximum 150 mg)	Placebo	Significantly lower plasma HMMA AUC_{0-3h} in African-American participants after the low dose. The same was found for females. No AEs of concern were reported, and no interventions were required. No SAEs reported. [543, 567, 710, 711]
DA05707 and DA017964	Double-blind, randomized, placebo-controlled within subjects Double-blind-randomized counterbalanced (within-subjects) study	9	7/2 (M/F) Age range 18-24	1.0 mg/kg, 1.6 mg/kg (maximum 150 mg)	Placebo	No AEs of concern were reported, and no interventions required. No SAEs reported. [248, 250]

Funding/grants/ support	Study design	Sample given MDMA[A]	Demographics	Dose of MDMA	Comparator	Safety findings
DA01696, DA12393, DA00053 (R.T.J.), National Institute on Drug Abuse Grants DA00064, DA14528 (J.H.M.), Division of Research Resources, National Institutes of Health Grant 5 M01 RR-00079	Double-blind crossover (within-subjects), ascending dose	8	5/3 (M/F) Age range 24-39, Average age 29	0.5 mg/kg; 1.5 mg/kg	Placebo (lactose) In Lester et al. 2000, compared cardiac data with ascending doses of dobutamine	No AEs of concern reported, and no interventions required. No SAEs reported. [20, 40]
No grant numbers listed; supported by the Swiss Federal Office of Public Health, Bern, Switzerland, and the Heffter Research Institute.	Randomized, placebo-controlled, within-subjects, (placebo/pindolol, placebo/MDMA)	15	15/0 (M/F) Average age 24.3	1.6 mg/kg	Placebo, pindolol pretreatment	No information on AEs reported; no SAEs reported. [184, 712]
DA01696, DA12393, DA00053 (R.T.J.), National Institute on Drug Abuse Grants DA00064, DA14528 (J.H.M.), Division of Research Resources, National Institutes of Health Grant 5 M01 RR-00079	Double-blind crossover (within-subjects), ascending dose	8	5/3 (M/F) Age range 24-39, Average age 29	0.5 mg/kg; 1.5 mg/kg	Placebo (lactose), ascending doses of dobutamine	No AEs of concern reported, and no interventions required. No SAEs reported. [20, 40]
Supported by Heffter Research Institute, no grant numbers	Randomized, double-blind controlled within-subjects	16	10/6 (M/F) Average age 26	1.7 mg/kg	Placebo	No AEs of concern reported, no intervention required. No SAEs reported. [599, 713]

Funding/grants/ support	Study design	Sample given MDMA[A]	Demographics	Dose of MDMA	Comparator	Safety findings
	(crossover) design, EEG in both					
Supported by Heffter Research Institute, no grant numbers	Randomized, placebo-controlled within-subjects, pre-administered drug, MDMA	16	12/4 (M/F) Average age 27.4	1.5 mg/kg	Placebo, 40 mg citalopram i.v. pretreatment	No AEs of concern reported, no intervention required. No SAEs reported. [576, 577]
Supported by Heffter Research Institute, no grant numbers	Randomized, placebo-controlled within-subjects, pre-administered drug, MDMA	14	13/1 (M/F) Average age 26	1.5 mg/kg	Placebo, 50 mg p.o ketanserin pretreatment	No AEs of concern reported, no intervention required. No SAEs reported. [580]
Supported by Heffter Research Institute, no grant numbers	Randomized, placebo-controlled within-subjects, pre-administered drug, MDMA)	13	9/4 (M/F) Average age 26	1.5 mg/kg	Placebo, 1.4 mg haloperidol pretreatment	No AEs of concern reported, no intervention required. No SAEs reported. [586]
None listed, acknowledges "SBG Medical Science Foundation, Switzerland" and Heffter Research institute	Double-blind, placebo-controlled crossover (within-subjects)	16	13/3 (M/F) Average age 29	1.7 mg/kg	Placebo	One individual showed increased BP of 240/145 SBP/DBP, resolved with no medical intervention needed. Changes in BP significant for SBP, not for DBP but present. [23, 714]
No grants or NCTs listed	Observational, from psychiatric treatment by Swiss psychiatrists when MDMA treatment allowed	2	1/1 (M/F) Age range 24-40	1.7 mg/kg 1.5 mg/kg	None	No information on AEs of concern reported; no SAEs reported. [546, 547]
No grants or NCTs listed	Open-label, single dose, also baseline to post-administration	8	8/0 (M/F) Age range 22-32	40 mg (~0.57 mg/kg)	Placebo	No AEs of concern reported, and no interventions required. No SAEs reported. [150, 231, 369]

Funding/grants/ support	Study design	Sample given MDMA[A]	Demographics	Dose of MDMA	Comparator	Safety findings
DA06863, MH00534, RR00425	Placebo controlled, double-blind study, with two ascending doses MDMA per subject	18	12/6 (M/F) Age range 20-62	0.25 mg/kg to 2.5 mg/kg in 0.25 mg/kg increments; each person received 2 ascending doses	Placebo	No AEs of concern were reported, and no interventions required. No SAEs were reported. [43, 44, 715]
No grants or funding listed	Open label / naturalistic, in context of ongoing psychotherapy	29	Not specified	75-150 mg (~1.1 -2.1 mg/kg), 200 mg (~2.9 mg/kg) half-dose offered later	None	No AEs of concern reported, and no interventions required. No SAEs reported. [54]
No grants or funding listed	Open label single administration	21	13/8 (M/F) Age range 20-58	Varied, self-selected, 0.8 mg/lb, average 1.14 mg/lb (app. 2.5 mg/kg)	None	No AEs of concern reported, no interventions required. No SAEs reported. [39]

Appendix Table 2: Pre-Drug, Peak, and Final Body Temperature (ºC) During Experimental Sessions with Placebo or any MDMA Dose in MAPS-Sponsored MAA-1

Dose	N	Pre-drug Mean (SD) Min/Max	Peak Mean (SD) Min/Max	Final Mean (SD) Min/Max	N (%) with 1 ° C above Pre-Drug
Placebo	4	36.5 (0.23) 36.1/36.8	36.8 (0.12) 36.6/36.9	36.7 (0.20) 36.4/36.9	0
75 mg	4	36.6 (0.45) 36.2/37.2	37.2 (0.29) 36.9/37.6	37.0 (0.19) 36.7/37.2	0
100 mg	7	36.6 (0.50) 35.9/37.3	37.3 (0.33) 36.7/37.7	37.2 (0.31) 36.6/37.6	2 (28.6)
125 mg	4	37.1 (0.23) 36.8/37.4	37.4 (0.26) 37.2/37.7	37.3 (0.08) 37.2/37.4	0
Open-label (75 mg)	4	36.7 (0.26) 36.4/36.9	37.2 (0.35) 36.7/37.6	37.1 (0.35) 36.7/37.6	0
Open-label (125 mg)	4	36.6 (0.19) 36.4/36.9	37.2 (0.26) 36.8/37.4	36.9 (0.36) 36.4/37.2	0

Appendix Table 3: Pre-Drug, Peak, and Final Body Temperature (ºC) During Experimental Sessions with Placebo or Full MDMA Dose in MAPS-Sponsored MDA-1 Study

Dose	N	Pre-drug Mean (SD) Min/Max	Peak Mean (SD) Min/Max	Final Mean (SD) Min/Max	N (%) with BT 1 ° C above Pre-Drug
Placebo	5	36.4 (0.43) 35.7/36.9	36.9 (0.27) 36.5/37.5	36.4 (0.56) 35.0/37.0	1 (20.0)
125 mg	13	36.3 (0.49) 35.6/37.4	37.3 (0.71) 36.1/39.9	36.9 (0.44) 35.9/37.6	7 (53.8)
Open-label (125 mg)	17	36.3 (0.44) 35.4/37.2	37.3 (0.33) 36.6/38.0	36.9 (0.39) 36.0/37.4	9 (52.9)

Appendix Table 4: Pre-drug, Peak, and Final Systolic Blood Pressure During Experimental Sessions with Placebo or any MDMA Dose in MAPS-Sponsored MAA-1 Study

Dose	N	Pre-drug Mean (SD) Min/Max	Peak Mean (SD) Min/Max	Final Mean (SD) Min/Max	N (%) with SBP Above 180 mm Hg
Placebo	4	131.0 (11.6) 112.0/144.0	142.5 (11.8) 126.0/159.0	126.9 (5.6) 121.0/138.0	0
75 mg	4	117.5 (14.8) 101.0/137.0	136.3 (26.3) 116.0/174.0	122.0 (10.7) 112.0/134.0	0
100 mg	7	113.3 (12.9) 92.0/133.0	121.4 (9.4) 113.0/141.0	114.6 (10.2) 105.0/135.0	0
125 mg	4	114.8 (5.1) 109.0/120.0	123.5 (14.6) 110.0/143.0	114.0 (4.1) 111.0/120.0	0
Open-label 75 mg	4	124 (11.0) 116.0/140.0	138.8 (17.0) 127.0/164.0	131.8 (17.6) 114.0/156.0	0
Open-label 125 mg	4	131.0 (3.9) 126.0/135.0	153.0 (17.6) 135.0/170.0	142.8 (19.1) 127.0/170.0	0

Appendix Table 5: Pre-drug, Peak, and Final Systolic Blood Pressure During Experimental Sessions with Placebo or Full MDMA Dose in MAPS-Sponsored MDA-1 Study

Dose	N	Pre-drug Mean (SD) Min/Max	Peak Mean (SD) Min/Max	Final Mean (SD) Min/Max	N (%) with SBP Above 180 mm Hg
Placebo	5	127.5 (13.34) 102.0/145.0	146.0 (15.53) 126.0/173.0	119.7 (8.71) 106.0/135.0	2 (40.0)
125 mg	13	129.9 (17.94) 91.0/178.0	157.54 (17.05) 127.0/192.0	125.69 (11.45) 103.0/145.0	7 (53.8)
Open-label 125 mg	17	129.1 (19.13) 78.0/162.0	157.0 (18.64) 119.0/196.0	128.0 (13.8) 106.0/153.0	5 (29.4)

Appendix Table 6: Pre-drug, Peak, and Final Diastolic Blood Pressure During Experimental Sessions with Placebo or any MDMA Dose in MAPS-Sponsored MAA-1 Study

Dose	N	Pre-drug Mean (SD) Min/Max	Peak Mean (SD) Min/Max	Final Mean (SD) Min/Max	N (%) with DBP Above 110 mm Hg
Placebo	4	76.9 (10.0) 64.0/89.0	82.3 (11.2) 72.0/106.0	74.5 (8.6) 62.0/88.0	0
75 mg	4	68.5 (9.3) 61.0/81.0	80.3 (5.3) 73.0/85.0	68.8 (4.6) 64.0/74.0	0
100 mg	7	60.7 (6.3) 52.0/72.0	76.9 (8.4) 62.0/89.0	67.1 (8.5) 59.0/82.0	0
125 mg	4	67.8 (2.2) 66.0/71.0	78.3 (9.0) 69.0/86.0	68.5 (3.4) 64.0/72.0	0
Open-label 75 mg	4	71.0 (10.8) 62.0/85.0	82.5 (4.7) 77.0/88.0	72.0 (3.5) 69.0/75.0	0
Open-label 125 mg	4	81.5 (8.3) 70.0/88.0	88.3 (7.6) 79.0/95.0	73.0 (7.6) 62.0/78.0	0

Appendix Table 7: Pre-drug, Peak, and Final Diastolic Blood Pressure During Experimental Sessions with Placebo or any MDMA Dose in MAPS-Sponsored MDA-1 Study

Dose	N	Pre-drug Mean (SD) Min/Max	Peak Mean (SD) Min/Max	Final Mean (SD) Min/Max	N (%) with DBP Above 120 mm Hg
Placebo	5	78.5 (16.49) 4.06/94.0	91.6 (13.40) 72/112	78.4 (11.40) 64/100	1 (20.0)
125 mg	13	78.7 (11.05) 55.0/106.0	93.9 (19.11) 75.0/154.0	73.1 (7.47) 58.0/84.0	4 (30.8)
Open-label 125 mg	17	81.1 (16.09) 50.0/117.0	94.6 (11.69) 72.0/118.0	77.5 (12.66) 52.0/97.0	2 (11.8)

Appendix Table 8: Pre-drug, Peak, and Final Heart Rate During Experimental Sessions with Placebo or any MDMA Dose in MAPS-Sponsored MAA-1 Study

Dose	N	Pre-drug Mean (SD) Min/Max	Peak Mean (SD) Min/Max	Final Mean (SD) Min/Max	N (%) with HR Above 110 BPM
Placebo	4	57.3 (9.7) 47.0/78.0	75.3 (10.3) 63.0/94.0	67.4 (7.4) 59.0/83.0	0
75 mg	4	68.0 (3.7) 63.0/72.0	87.0 (14.0) 75.0/105.0	73.8 (6.3) 65.0/80.0	0
100 mg	7	70.0 (12.2) 53.0/88.0	89.3 (12.1) 71.0/105.0	79.1 (15.9) 58.0/100.0	0
125 mg	4	78.5 (12.1) 61.0/88.0	95.0 (19.8) 75.0/114.0	89.3 (13.2) 75.0/101.0	1 (25.0)
Open-label 75 mg	4	58.0 (6.1) 52.0/65.0	71.8 (10.1) 58.0/82.0	66.5 (7.1) 57.0/74.0	0
Open-label 125 mg	4	64.0 (6.9) 58.0/74.0	87.0 (8.1) 80.0/94.0	70.0 (6.2) 63.0/78.0	0

Appendix Table 9: Pre-drug, Peak, and Final Heart Rate During Experimental Sessions with Placebo or any MDMA Dose in MAPS-Sponsored MDA-1 Study

Dose	N	Pre-drug Mean (SD) Min/Max	Peak Mean (SD) Min/Max	Final Mean (SD) Min/Max	N (%) with HR Above 120 BPM
Placebo	5	69.0 (13.88) 50.0/100.0	81.5 (12.26) 71.0/108.0	71.4 (7.11) 60.0/86.0	0
125 mg	13	69.3 (10.74) 53.0/95.0	105.5 (14.44) 89.0/133.0	92.9 (16.43) 69.0/133.0	6 (46.2)
Open-label 125 mg	17	70.3 (10.23) 57.0/91.0	106.8 (17.34) 77.0/140.0	87.1 (13.97) 62.0/117.0	6 (35.3)

Appendix Table 10: Summary of Lifetime and Baseline Positive and Serious Responses on C-SSRS for Study MAA-1

		Lifetime [a] N (%)	Pre-drug Exposure [b] N (%)
Social Anxiety in Autistic Adults			
Blinded Placebo	PI	3 (75.0)	0
	SI	0	0
	PB	1 (25.0)	0
	O	4	8
	N	4	4
Blinded Active Doses (75-125 mg)	PI	4 (50.0)	0
	SI	1 (12.5)	0
	PB	1 (12.5)	0
	O	8	16
	N	8	8

PI=Positive Ideation, SI=Serious Ideation, PB=Positive Behavior, O=Observations, N=Number of Participants

[a] Lifetime accounts for all suicidal ideation and behavior prior to study Visit 1, according to participant recall and medical records.

[b] Pre-drug exposure represents measures taken during Preparatory Sessions and before drug administration in Experimental Session 1.

Appendix Table 11: C-SSRS Positive and Serious Responses During Experimental Sessions and Integrative Session 1, Day 2 Phone Call, and Day 7 Phone Call Post-Drug for Study MAA-1

Dose		Session 1 N (%)					Session 2 N (%)				
		Pre-drug [a]	During-drug [b]	Integrative Session 1	Day 2	Day 7	Pre-drug [a]	During-drug [b]	Integrative Session 1	Day 2	Day 7
Social Anxiety in Autistic Adults											
Blinded Placebo	PI	0	0	0	0	0	0	0	0	0	0
	SI	0	0	0	0	0	0	0	0	0	0
	PB	0	0	0	0	0	0	0	0	0	0
	N	4	4	4	4	3	3	3	4	4	4
Blinded Active Dose (75-125 mg)	PI	0	1 (14.3)	1 (12.5)	0	0	0	0	0	0	0
	SI	0	0	0	0	0	0	0	0	0	0
	PB	0	0	0	0	0	0	0	0	0	0
	N	8	7	8	8	8	8	6	7	7	7
Open-label Stage 2 Active Dose (75-125 mg)	PI	1 (25.0)	0	0	0	0	0	0	0	0	0
	SI	0	0	0	0	0	0	0	0	0	0
	PB	0	0	0	0	0	0	0	0	0	0
	N	4	4	4	4	4	4	3	4	4	3

PI=Positive Ideation, SI=Serious Ideation, PB=Positive Behavior, N=Number of Participants

[a] Pre-drug measurement taken day of Experimental Session prior to drug administration.

[b] During-drug observation measured at Experimental Session endpoint, approximately 6 hours after drug administration.

Appendix Table 12: C-SSRS Positive Responses at Endpoints After Treatment for Study MAA-1

		Primary/ Secondary Endpoint N (%)	Long-term Follow-up N (%)
Social Anxiety in Autistic Adults			
Blinded	PI	1 (25.0)	2 (50.0)
Placebo	SI	0	0
	PB	0	0
	N	4	4
Blinded	PI	2 (28.6)	0
Active Doses	SI	0	0
(75-125 mg)	PB	0	0
	N	7	7

PI=Positive Ideation, SI=Serious Ideation, PB=Positive Behavior, N=Number of Participants

Appendix Table 13: Summary of Lifetime and Baseline Positive and Serious Responses on C-SSRS for Study MDA-1

		Lifetime [a] N (%)	Pre-drug Exposure [b] N (%)
Anxiety Associated with a Life-threatening Illness			
Blinded	PI	4 (80.0)	5 (25.0)
Placebo	SI	1 (20.0)	0
	PB	0	1 (5.0)
	O	5	20
	N	5	5
Blinded	PI	10 (76.9)	0
Active Dose	SI	0	0
(125 mg)	PB	3 (23.1)	0
	O	13	52
	N	13	13

PI=Positive Ideation, SI=Serious Ideation, PB=Positive Behavior, O=Observations, N=Number of Participants

[a] Lifetime accounts for all suicidal ideation and behavior prior to study Visit 1, according to participant recall and medical records.

[b] Pre-drug exposure represents measures taken during Preparatory Sessions and before drug administration in Experimental Session 1.

Appendix Table 14: C-SSRS Positive and Serious Responses During Experimental Sessions and 1-Day Post-Drug for Study MDA-1

Dose		Session 1 N (%)			Session 2 N (%)			Session 3 N (%)		
		Pre-drug [a]	During-drug [b]	Integration Day 1	Pre-drug [a]	During-drug [b]	Integration Day 1	Pre-drug [a]	During-drug [b]	Integration Day 1
Anxiety Associated with a Life-threatening Illness										
Blinded	PI	0	0	0	0	0	0	---	---	---
Placebo	SI	0	0	0	0	0	0			
	PB	0	0	0	0	0	0			
	N	5	5	5	5	5	5			
Blinded	PI	0	0	0	0	0	0	0	0	0
Active Dose	SI	0	0	0	0	0	0	0	0	0
(125 mg)	PB	0	0	0	0	0	0	0	0	0
	N	13	13	13	13	13	13	11	10	12
Open-label	PI	0	0	0	0	0	0	0	0	0
Stage 2	SI	0	0	0	0	0	0	0	0	0
Active Dose	PB	0	0	0	0	0	0	0	0	0
(125 mg)	N	5	5	5	5	5	5	5	5	5

PI=Positive Ideation, SI=Serious Ideation, PB=Positive Behavior, N=Number of Participants

[a] Pre-drug measurement taken day of Experimental Session prior to drug administration.

[b] During-drug observation measured at Experimental Session endpoint, approximately 6 hours after drug administration.

Appendix Table 15: C-SSRS Positive Responses During Telephone Contact Following Experimental Sessions for Study MDA-1

		Session 1 N (%)		Session 2 N (%)		Session 3 N (%)	
		Day 2	Day 7	Day 2	Day 7	Day 2	Day 7
Anxiety Associated with a Life-threatening Illness							
Blinded	PI	0	0	0	0	---	---
Placebo	SI	0	0	0	0		
	PB	0	0	0	0		
	N	5	5	5	5		
Blinded	PI	0	0	0	0	0	0
Active Dose	SI	0	0	0	0	0	0
(125 mg)	PB	0	0	0	0	0	0
	N	13	13	13	13	12	12
Open-label	PI	0	0	0	0	0	0
Stage 2 Doses	SI	0	0	0	0	0	0
(100-125 mg)	PB	0	0	0	0	0	0
	N	5	5	5	5	5	5

PI=Positive Ideation, SI=Serious Ideation, PB=Positive Behavior, N=Number of Participants

Appendix Table 16: C-SSRS Positive Responses at Endpoints After Treatment for Study MDA-1

Dose		Primary/ Secondary Endpoint N (%)	End of Stage 1/ End of Stage 2 N (%)	Long-term Follow-up N (%)
Anxiety Associated with a Life-threatening Illness				
Blinded	PI	0	---	1 (20.0)
Placebo	SI	0		0
	PB	0		0
	N	5		5
Blinded	PI	1 (7.7)	0	0
Active Dose	SI	0	0	0
(125 mg)	PB	0	0	0
	N	13	12	12
Open-label	PI	0	0	---
Stage 2 Doses	SI	0	0	
(100-125 mg)	PB	0	0	
	N	5	5	

PI=Positive Ideation, SI=Serious Ideation, PB=Positive Behavior, N=Number of Participants

Appendix Table 17: Prevalence of Spontaneously Reported Reactions During Experimental Sessions and Telephone Contact on Day 1-7 After Experimental Sessions in Sponsor-Supported Phase 2 Study MAA-1

Post-drug	Day 0 N (%)	Day 1 N (%)	Day 2 N (%)	Day 3 N (%)	Day 4 N (%)	Day 5 N (%)	Day 6 N (%)	Day 7 N (%)
Anxiety								
Placebo (N=4)	1 (25.0)	---	1 (25.0)	---	---	---	---	---
75-125 mg (N=8)	6 (75.0)	1 (12.5)	---	---	---	---	---	---
Open-label (N=4)	1 (25.0)	---	---	---	---	---	---	---
Diarrhea								
Placebo (N=4)	---	---	---	---	---	---	---	---
75-125 mg (N=8)	---	---	---	---	---	---	---	---
Open-label (N=4)	1 (25.0)	---	---	---	---	---	---	---
Difficulty Concentrating								
Placebo (N=4)	1 (25.0)	---	---	---	---	---	---	---
75-125 mg (N=8)	5 (62.5)	1 (12.5)	3 (37.5)	1 (12.5)	---	---	1 (12.5)	---
Open-label (N=4)	2 (50.0)	---	---	---	---	---	---	---
Dizziness								
Placebo (N=4)	1 (25.0)	---	---	---	---	---	1 (25.0)	1 (25.0)
75-125 mg (N=8)	1 (12.5)	---	---	---	---	---	---	---
Open-label (N=4)	---	---	---	---	---	---	---	---
Drowsiness								
Placebo (N=4)	---	---	---	---	---	---	---	---
75-125 mg (N=8)	1 (12.5)	---	---	---	---	---	1 (12.5)	---
Open-label (N=4)	1 (25.0)	---	---	---	---	---	---	---
Dry Mouth								

Post-drug	Day 0 N (%)	Day 1 N (%)	Day 2 N (%)	Day 3 N (%)	Day 4 N (%)	Day 5 N (%)	Day 6 N (%)	Day 7 N (%)
Placebo (N=4)	---	---	---	---	---	---	---	---
75-125 mg (N=8)	---	---	---	---	---	---	---	---
Open-label (N=4)	---	---	---	---	---	---	---	---
Fatigue								
Placebo (N=4)	1 (25.0)	---	2 (50.0)	---	---	---	---	---
75-125 mg (N=8)	4 (50.0)	3 (37.5)	3 (37.5)	1 (12.5)	---	---	1 (12.5)	---
Open-label (N=4)	---	2 (50.0)	3 (75.0)	---	---	1 (25.0)	1 (25.0)	1 (25.0)
Headache								
Placebo (N=4)	1 (25.0)	1 (25.0)	1 (25.0)	---	---	---	---	---
75-125 mg (N=8)	4 (50.0)	3 (37.5)[A]	2 (25.0)	---	---	3 (37.5)	2 (25.0)	1 (12.5)
Open-label (N=4)	---	1 (25.0)	1 (25.0)	---	---	1 (25.0)	---	---
Heavy Legs								
Placebo (N=4)	---	---	---	---	---	---	---	---
75-125 mg (N=8)	---	---	---	---	---	---	---	---
Open-label (N=4)	---	---	---	---	---	---	---	---
Impaired Gait/Balance								
Placebo (N=4)	---	---	---	---	---	---	---	---
75-125 mg (N=8)	1 (12.5)	---	---	---	---	---	---	---
Open-label (N=4)	---	---	---	---	---	---	---	---
Impaired Judgment								
Placebo (N=4)	---	---	---	---	---	---	---	---
75-125 mg (N=8)	---	---	---	---	---	---	---	---

Post-drug	Day 0 N (%)	Day 1 N (%)	Day 2 N (%)	Day 3 N (%)	Day 4 N (%)	Day 5 N (%)	Day 6 N (%)	Day 7 N (%)
Open-label (N=4)	---	---	---	---	---	---	---	---
Increased Irritability								
Placebo (N=4)	---	---	1 (25.0)	---	---	---	---	---
75-125 mg (N=8)	1 (12.5)	---	---	---	---	1 (12.5)	---	---
Open-label (N=4)	---	---	---	---	---	---	---	---
Insomnia								
Placebo (N=4)	---	---	---	---	---	---	---	---
75-125 mg (N=8)	---	1 (12.5)	1 (12.5)	1 (12.5)	---	1 (12.5)	1 (12.5)	---
Open-label (N=4)	---	1 (25.0)	1 (25.0)	---	---	---	---	---
Tight Jaw								
Placebo (N=4)	---	---	1 (25.0)	---	---	---	---	1 (25.0)
75-125 mg (N=8)	1 (12.5)	---	---	---	---	---	---	---
Open-label (N=4)	---	1 (25.0)	---	---	---	---	---	---
Lack of Appetite								
Placebo (N=4)	1 (25.0)	---	---	---	---	---	---	---
75-125 mg (N=8)	3 (37.5)	3 (37.5)	1 (12.5)	---	---	---	---	---
Open-label (N=4)	3 (75.0)	---	---	---	---	---	---	---
Low Mood								
Placebo (N=4)	---	---	1 (25.0)	---	---	---	2 (50.0)	1 (25.0)
75-125 mg (N=8)	2 (25.0)	2 (25.0)	4 (50.0)	---	---	1 (12.5)	1 (12.5)	1 (12.5)
Open-label (N=4)	---	1 (25.0)	1 (25.0)	---	---	---	---	1 (25.0)
Muscle Tension								
Placebo (N=4)	1 (25.0)	---	---	---	---	---	---	---

Post-drug	Day 0 N (%)	Day 1 N (%)	Day 2 N (%)	Day 3 N (%)	Day 4 N (%)	Day 5 N (%)	Day 6 N (%)	Day 7 N (%)
75-125 mg (N=8)	3 (37.5)	---	---	---	---	---	---	---
Open-label (N=4)	2 (50.0)	---	---	---	---	1 (25.0)	---	---
Nausea								
Placebo (N=4)	---	---	---	---	---	---	---	---
75-125 mg (N=8)	---	---	---	---	---	---	---	---
Open-label (N=4)	---	---	---	---	---	---	---	---
Need More Sleep								
Placebo (N=4)	---	1 (25.0)	1 (25.0)	---	---	---	---	---
75-125 mg (N=8)	1 (12.5)	2 (25.0)	---	1 (12.5)	---	---	---	---
Open-label (N=4)	---	3 (75.0)	2 (50.0)	---	---	---	---	---
Nystagmus								
Placebo (N=4)	---	---	---	---	---	---	---	---
75-125 mg (N=8)	---	---	---	---	---	---	---	---
Open-label (N=4)	---	---	---	---	---	---	---	---
Parasthesia								
Placebo (N=4)	---	---	---	---	---	---	---	---
75-125 mg (N=8)	---	1 (12.5)	---	---	---	---	---	---
Open-label (N=4)	1 (25.0)	1 (25.0)	---	---	---	---	---	---
Perspiration								
Placebo (N=4)	1 (25.0)	---	---	---	---	---	---	---
75-125 mg (N=8)	1 (12.5)	---	---	---	---	---	---	---
Open-label (N=4)	2 (50.0)	---	---	---	---	---	---	---

Post-drug	Day 0 N (%)	Day 1 N (%)	Day 2 N (%)	Day 3 N (%)	Day 4 N (%)	Day 5 N (%)	Day 6 N (%)	Day 7 N (%)
Restlessness								
Placebo (N=4)	1 (25.0)	---	---	---	---	---	---	---
75-125 mg (N=8)	3 (37.5)	---	---	---	---	---	---	---
Open-label (N=4)	1 (25.0)	---	1 (25.0)	---	---	---	---	---
Ruminations								
Placebo (N=4)	---	---	---	---	---	---	1 (25.0)	---
75-125 mg (N=8)	1 (12.5)	---	---	---	---	---	---	---
Open-label (N=4)	2 (50.0)	---	---	---	---	---	---	---
Sensitivity to Cold								
Placebo (N=4)	---	---	---	---	---	---	---	1 (25.0)
75-125 mg (N=8)	4 (50.0)	---	---	---	---	---	---	---
Open-label (N=4)	---	---	---	---	---	---	---	---
Thirst								
Placebo (N=4)	---	---	---	---	---	---	---	---
75-125 mg (N=8)	2 (25.0)	1 (12.5)	---	---	---	---	---	---
Open-label (N=4)	---	---	---	---	---	---	---	---
Weakness								
Placebo (N=4)	1 (25.0)	---	1 (25.0)	---	---	---	---	---
75-125 mg (N=8)	1 (12.5)	1 (12.5)	1 (12.5)	---	---	---	---	---
Open-label (N=4)	---	---	1 (25.0)	---	---	---	---	---

[a]Severe reaction='Headache' on Day 1 in a participant in the active dose group (75-125 mg)

Appendix Table 18: Prevalence of Spontaneously Reported Reactions During Experimental Sessions in MDA-1

Dose	Number of Participants (%)[1]		
	Placebo (N=5)	125 mg (N=13)	Open-label (N=17)
Anxiety	---	3 (23.1)	2 (11.8)
Diarrhea	---	---	---
Difficulty Concentrating	---	---	---
Dizziness	---	---	---
Drowsiness	---	1 (7.7)	3 (17.6)
Dry Mouth	1 (20.0)	9 (69.2)	8 (47.1)
Fatigue	---	2 (15.4)	5 (29.4)
Headache	1 (20.0)	8 (61.5)	4 (23.5)
Heavy Legs	---	---	---
Impaired Gait/Balance	---	---	1 (5.9)
Impaired Judgment	---	---	---
Increased Irritability	---	---	---
Insomnia	1 (20.0)	2 (15.4)	4 (23.5)
Tight Jaw	1 (20.0)	11 (84.6)	15 (88.2)
Lack of Appetite	---	4 (30.8)	7 (41.2)
Low Mood	---	1 (7.7)	---
Muscle Tension	---	---	---
Nausea	1 (20.0)	3 (23.1)	4 (23.5)
Need More Sleep	---	---	---
Nystagmus	---	1 (7.7)	2 (11.8)
Parasthesia	---	1 (7.7)	1 (5.9)
Perspiration	---	9 (69.2)	7 (41.2)
Restlessness	---	2 (15.4)	2 (11.8)
Ruminations	---	---	---
Sensitivity to Cold	1 (20.0)	2 (15.4)	2 (11.8)
Thirst	2 (40.0)	11 (84.6)	9 (52.9)
Weakness	---	---	1 (5.9)

[1] No severe reactions reported.

Appendix Table 19: Relative Incidence of Spontaneously Reported Reactions During Telephone Contact on Day 1-7 After Experimental Sessions in MDA-1

Post-drug	Day 1 N (%)	Day 2 N (%)	Day 3 N (%)	Day 4 N (%)	Day 5 N (%)	Day 6 N (%)	Day 7 N (%)
Anxiety							
Placebo (N=5)	---	1 (20.0)	2 (40.0)	---	1 (20.0)	---	1 (20.0)
125 mg (N=13)	4 (30.8)	3 (23.1)	4 (30.8)	4 (30.8)	1 (7.7)	2 (15.4)	4 (30.8)
Open-label (N=17)	1 (5.9)	5 (29.4)	5 (29.4)	5 (29.4)	4 (23.5)	5 (29.4)	1 (5.9)
Diarrhea							
Placebo (N=5)	---	---	---	---	---	1 (20.0)	---
125 mg (N=13)	---	---	---	---	---	---	1 (7.7)
Open-label (N=17)	---	1 (5.9)[a]	---	---	1 (5.9)	---	---
Difficulty Concentrating							
Placebo (N=5)	---	---	---	---	---	---	---
125 mg (N=13)	---	1 (7.7)	2 (15.4)	---	---	---	---
Open-label (N=17)	2 (11.8)	3 (17.6)	3 (17.6)	---	---	---	---
Dizziness							
Placebo (N=5)	---	---	---	---	---	---	---
125 mg (N=13)	---	---	---	---	---	---	---
Open-label (N=17)	1 (5.9)	---	---	---	---	---	---
Drowsiness							
Placebo (N=5)	---	---	1 (20.0)	---	---	---	---
125 mg (N=13)	4 (30.8)	---	1 (7.7)	---	---	---	---
Open-label (N=17)	1 (5.9)	2 (11.8)	1 (5.9)	1 (5.9)	---	---	---
Dry Mouth							
Placebo (N=5)	---	---	---	---	---	---	---
125 mg (N=13)	2 (15.4)	1 (7.7)	1 (7.7)	---	---	---	---
Open-label (N=17)	3 (17.6)	2 (11.8)	---	---	---	---	---
Fatigue							
Placebo (N=5)	---	2 (40.0)	1 (20.0)	2 (40.0)	---	---	---
125 mg (N=13)	6 (46.2)	9 (69.2)	12 (92.3)	8 (61.5)	8 (61.5)	6 (46.2)	5 (38.5)
Open-label (N=17)	7 (41.2)	13 (76.5)	10 (58.8)	5 (29.4)	7 (41.2)	2 (11.8)	---
Headache							
Placebo (N=5)	2 (40.0)	1 (20.0)	1 (20.0)	1 (20.0)	---	---	---
125 mg (N=13)	6 (46.2)	4 (30.8)	2 (15.4)	2 (15.4)	---	---	---
Open-label (N=17)	7 (41.2)	5 (29.4)	2 (11.8)	2 (11.8)	2 (11.8)	1 (5.9)	---

Post-drug	Day 1 N (%)	Day 2 N (%)	Day 3 N (%)	Day 4 N (%)	Day 5 N (%)	Day 6 N (%)	Day 7 N (%)
Heavy Legs							
placebo (N=5)	---	---	---	---	---	---	---
125 mg (N=13)	---	---	---	---	---	---	---
Open-label (N=17)	---	---	---	---	---	---	---
Impaired Gait/Balance							
Placebo (N=5)	---	---	---	---	---	---	---
125 mg (N=13)	---	1 (7.7)	---	---	1 (7.7)	1 (7.7)	---
Open-label (N=17)	1 (5.9)	---	---	---	---	---	---
Impaired Judgment							
Placebo (N=5)	---	---	---	---	---	---	---
125 mg (N=13)	---	---	---	---	---	---	---
Open-label (N=17)	---	---	---	---	---	---	---
Increased Irritability							
Placebo (N=5)	---	---	---	---	1 (20.0)	1 (20.0)	1 (20.0)
125 mg (N=13)	---	---	---	---	1 (7.7)	2 (15.4)	1 (7.7)
Open-label (N=17)	---	---	---	---	---	---	2 (11.8)
Insomnia							
Placebo (N=5)	---	---	2 (40.0)	1 (20.0)	---	---	---
125 mg (N=13)	6 (46.2)	2 (15.4)	2 (15.4)	---	---	---	---
Open-label (N=17)	3 (17.6)	4 (23.5)	1 (5.9)	2 (11.8)	---	2 (11.8)	3 (17.6)
Tight Jaw							
Placebo (N=5)	1 (20.0)	---	---	---	---	---	---
125 mg (N=13)	7 (53.8)	4 (30.8)	3 (23.1)	1 (7.7)	---	---	---
Open-label (N=17)	9 (52.9)	8 (47.1)	4 (23.5)	3 (17.6)	2 (11.8)	1 (5.9)	1 (5.9)
Lack of Appetite							
Placebo (N=5)	---	---	---	---	---	---	---
125 mg (N=13)	2 (15.4)	1 (7.7)	---	1 (7.7)	---	---	---
Open-label (N=17)	---	---	1 (5.9)	---	---	---	---
Low Mood							
Placebo (N=5)	---	1 (20.0)	1 (20.0)	1 (20.0)	3 (60.0)	1 (20.0)	2 (40.0)
125 mg (N=13)	3 (23.1)	5 (38.5)	5 (38.5)	1 (7.7)	3 (23.1)	2 (15.4)	2 (15.4)
Open-label (N=17)	1 (5.9)	5 (29.4)	7 (41.2)	1 (5.9)	5 (29.4)	3 (17.6)	1 (5.9)
Muscle Tension							
Placebo (N=5)	---	---	---	---	---	---	---
125 mg (N=13)	1 (7.7)	1 (7.7)	1 (7.7)	1 (7.7)	---	---	---

Post-drug	Day 1 N (%)	Day 2 N (%)	Day 3 N (%)	Day 4 N (%)	Day 5 N (%)	Day 6 N (%)	Day 7 N (%)
Open-label (N=17)	1 (5.9)	---	---	2 (11.8)	---	---	---
Nausea							
Placebo (N=5)	1 (20.0)	1 (20.0)	1 (20.0)	1 (20.0)	---	---	---
125 mg (N=13)	2 (15.4)	4 (30.8)	4 (30.8)	2 (15.4)	1 (7.7)	1 (7.7)	1 (7.7)
Open-label (N=17)	2 (11.8)	---	---	---	---	---	---
Need More Sleep							
Placebo (N=5)	1 (20.0)	1 (20.0)	---	---	---	---	1 (20.0)
125 mg (N=13)	5 (38.5)	6 (46.2)	6 (46.2)	2 (15.4)	1 (7.7)	2 (15.4)	---
Open-label (N=17)	1 (5.9)	7 (41.2)	5 (29.4)	2 (11.8)	2 (11.8)	1 (5.9)	1 (5.9)
Nystagmus							
Placebo (N=5)	---	---	---	---	---	---	---
125 mg (N=13)	---	---	---	---	---	---	---
Open-label (N=17)	---	---	---	---	---	---	---
Parasthesia							
Placebo (N=5)	---	---	---	---	---	---	---
125 mg (N=13)	---	1 (7.7)	---	---	---	---	---
Open-label (N=17)	---	---	---	---	---	---	---
Perspiration							
Placebo (N=5)	---	---	---	---	---	---	---
125 mg (N=13)	---	---	---	---	---	---	---
Open-label (N=17)	1 (5.9)	---	---	---	---	---	---
Restlessness							
Placebo (N=5)	---	---	1 (20.0)	---	1 (20.0)	1 (20.0)	1 (20.0)
125 mg (N=13)	1 (7.7)	---	---	---	1 (7.7)	---	---
Open-label (N=17)	---	---	---	1 (5.9)	1 (5.9)	---	---
Ruminations							
Placebo (N=5)	---	---	---	---	---	---	---
125 mg (N=13)	---	---	---	---	---	1 (7.7)	---
Open-label (N=17)	---	---	2 (11.8)	---	---	1 (5.9)	1 (5.9)
Sensitivity to Cold							
Placebo (N=5)	---	---	---	---	---	---	---
125 mg (N=13)	---	1 (7.7)	---	---	---	---	---
Open-label (N=17)	---	---	---	---	---	---	---
Thirst							
Placebo (N=5)	---	---	---	---	---	---	---

Post-drug	Day 1 N (%)	Day 2 N (%)	Day 3 N (%)	Day 4 N (%)	Day 5 N (%)	Day 6 N (%)	Day 7 N (%)
125 mg (N=13)	2 (15.4)	---	---	---	---	---	---
Open-label (N=17)	2 (11.8)	1 (5.9)	1 (5.9)	---	---	---	--
Weakness							
Placebo (N=5)	---	---	---	---	---	---	---
125 mg (N=13)	1 (7.7)	---	1 (7.7)	---	---	---	---
Open-label (N=17)	---	1 (5.9)	---	---	---	---	---

a One severe report of diarrhea on Day 2 contact. All other reactions were mild or moderate.

Appendix Table 20: Adverse Events by MedDRA (V. 17.1) System Organ Class (SOC) among Autistic Adults in Sponsor-Supported Phase 2 Study of MDMA-Assisted Psychotherapy MAA-1

SOC	Adverse Event Preferred Term[a]	Blinded Placebo	Blinded 75-125 mg	Open-label 75-125 mg	12-month Follow-up
Participants per dose group		4	8	4	11
Participants who reported an AE		1	4	3	3
		N (%)	**N (%)**	**N (%)**	**N (%)**
General disorders and administration site conditions					
	Pain	---	---	---	1 (9.0)
	Pyrexia	---	1 (12.5)	---	---
Gastrointestinal disorders					
	Irritable Bowel Syndrome	1 (25.0)	---	---	---
Infections and infestations					
	Nasopharyngitis	---	1 (12.5)	---	1 (9.0)
	Sinusitis	1 (25.0)	---	---	---
	Upper respiratory infection	1 (25.0)	1 (12.5)	1 (25.0)	---
Injury, poisonings, procedural complications					
	Ligament injury	---	1 (12.5)	---	---
	Retinal injury	---	---	---	1 (9.0)
Musculoskeletal and connective tissue disorders					
	Back pain	---	---	1 (25.0)	---
	Myalgia	---	---	1 (25.0)	---
Nervous system disorders					
	Headache	---	1 (12.5)	---	---
	Syncope	---	---	---	1 (9.0)
Psychiatric disorders					
	Anxiety	---	1 (12.5)	---	---
	Depressed mood	---	2 (25.0)	---	---
	Depression	1 (25.0)	1 (12.5)	---	---
	Dissociation	---	---	---	---
	Panic attack	---	1 (12.5)	1 (25.0)	---
	Panic reaction	---	1 (12.5)	---	---
	Psychiatric symptom	---	---	---	---
	Suicidal ideation	1 (25.0)	2 (25.0)	1 (25.0)	---
Reproductive system and breast disorders					
	Dysmennorhea	---	1 (12.5)	---	---
Respiratory, thoracic and mediastinal disorders					
	Cough	---	1 (12.5)	1 (25.0)	---
	Oropharyngeal pain	---	---	1 (25.0)	---

[a] Codes derived from MedDRA v17. Only one instance of an individual event per subject after each Experimental Session and dose is reported. No severe adverse events reported

Appendix Table 21: Adverse Events by MedDRA (v 17.1) System Organ Class (SOC) among Participants with Anxiety Associated with a Life-threatening Illness in Sponsor Supported Phase 2 Study of MDMA-Assisted Psychotherapy MDA-1

SOC	Adverse Event Preferred Term	Blinded Placebo	Blinded 125 mg	Open-label 125 mg	12-Month Follow-up
Participants per dose group		5	13	17	17
Participants who reported at least 1 AE		2	11	7	9
		N (%)	**N (%)**	**N (%)**	**N (%)**
Cardiac disorders					
	Arrhythmia	---	---	1 (5.9)	---
Gastrointestinal disorders					
	Abdominal discomfort	---	1 (7.7)	---	---
	Abdominal pain	---	1 (7.7)	---	---
	Aphthous stomatitis	1 (20.0)	---	---	---
	Esophageal pain [Oesophageal pain]	---	---	---	---
	Nausea	---	1 (7.7)	---	---
	Oesophageal pain	---	---	1 (5.9)	---
	Diarrhea [Diarhoea]	---	1 (7.7)	---	---
General disorders and administration site conditions					
	Chest pain	1 (20.0)	---	---	---
	Fatigue	---	3 (23.1)	---	---
	Pain	1 (20.0)	1 (7.7)	---	---
Infections and Infestations					
	Influenza	---	2 (15.4)	---	---
	Meningitis	---	---	---	1 (5.9)[+]
	Oral herpes	---	---	1 (5.9)	---
	Post procedural cellulitis	---	---	---	1 (5.9)
	Sepsis	---	---	---	1 (5.9)[+]
	Tinea infection	---	1 (7.7)	---	---
	Upper respiratory tract infection	---	---	1 (5.9)	---
	Viral upper respiratory tract infection	1 (20.0)	---	---	---
Injury, poisoning and procedural complications					
	Contusion	---	2 (15.4)	---	---
	Fall	---	1 (7.7)	---	---
	Skeletal injury	1 (20.0)	---	---	---
	Skin abrasion	---	1 (7.7)	---	---
	Thermal burn	1 (20.0)	---	---	---
	Tooth fracture	---	1 (7.7)	---	---
Investigations					
	Heart rate irregular	---	---	1 (5.9)	---
	Weight decrease	---	1 (7.7)	---	---
Musculoskeletal and connective tissue disorders					
	Arthralgia	---	1 (7.7)	---	---
	Back pain	---	2 (15.4)	---	---
	Intervertebral disc degeneration	---	---	---	1 (5.9)
	Plantar fasciitis	1 (20.0)	---	---	---
	Muscle spasms	1 (20.0)	---	---	---
	Scleroderma	---	---	---	1 (5.9)
	Tenosynovitis stenosans	---	1 (7.7)	---	---
Neoplasms benign, malignant and unspecified					
	Chordoma	---	1 (7.7)[+]	---	---
	Intraductal proliferative breast lesion	---	---	---	1 (5.9)
	Invasive ductal breast carcinoma	---	---	---	1 (5.9)[+]

Nervous system disorders					
	Aphasia	---	---	---	1 (5.9)[+]
	Balance disorder	---	1 (7.7)	---	---
	Cerebrovascular accident	---	---	---	1 (5.9)[+]
	Clumsiness	---	1 (7.7)	---	---
	Muscle contractions involuntary	1 (20.0)	---	---	---
	Neuropathy peripheral	1 (20.0)	---	1 (5.9)	1 (5.9)
	Paraesthesia	---	1 (7.7)	---	1 (5.9)
	Sciatica	---	---	---	1 (5.9)
	Sinus headache	---	1 (7.7)	---	---
	Spinal cord paralysis	---	---	---	1 (5.9)[+]
	Tremor	---	---	1 (5.9)	---
Psychiatric disorders					
	Anxiety	---	1 (7.7)	2 (11.8)	---
	Bruxism	---	---	1 (5.9)	---
	Depressed mood	---	1 (7.7)	1 (5.9)	---
	Depression	---	1 (7.7)	---	1 (5.9)
	Dissociation	---	1 (7.7)	---	---
	Drug abuse**	---	---	---	1 (5.9)
	Hypomania	---	---	1 (5.9)	---
	Insomnia	1 (20.0)	2 (15.4)	4 (23.5)	---
Renal and urinary disorders					
	Nephrolithias	---	1 (7.7)	---	---
Reproductive system and breast disorders					
	Vaginal discharge	---	1 (7.7)	---	---
Respiratory, thoracic and mediastinal disorders					
	Hyperventilation	---	1 (7.7)	---	---
Skin and subcutaneous tissue disorders					
	Alopecia	---	1 (7.7)	---	---
	Pruritis	---	---	1 (5.9)	---
	Urticaria	---	1 (7.7)	1 (5.9)	---
Vascular disorders					
	Hot flush	---	---	1 (5.9)	---
	Lymphoedema	---	---	---	1 (5.9)

[a]AEs coded using MedDRA v17. Each adverse event reported once per subject per blinded or open-label period.

[+]AEs rated severe. Of the seven AEs rated severe, six AEs occurred in a single individual after cancer reoccurrence. The participant's last visit was the Primary Endpoint. The subject died prior to LTFU. A second subject experienced a severe AE during the long-term follow-up.

**LLT was nondependent use of hallucinogens, not a drug abuse disorder

Appendix Table 22: Highlights of MDMA Clinical Pharmacology and Cardiac Safety

Therapeutic dose and exposure	Maximum proposed clinical dosing regimen: Three divided single-dose exposures spaced approximately a month apart of 80 mg -120 mg initial dose MDMA and 40 mg-60 mg supplemental half-dose MDMA, administered 1.5 to 2 hours after initial dose. Mean (%CV) C_{max} and AUC at the single maximum proposed clinical dose 125 mg MDMA [542]: C_{max}: 223.5±38.5 ng/mL (N=136) AUC: 948±172.9 ng*h/mL (N=136) Mean (%CV) C_{max} and AUC at the steady state with the maximum proposed clinical dosing regimen: Clinical dosing regimen does not reach steady state, single-dose only with at least 2 weeks washout between doses	
Maximum tolerated dose	NOAEL: 100 mg/kg (p.o.) in rat with single housing	
Maximum dose tested	Single Dose	150 mg
	Multiple Dose	The drug is designed to be given as a divided single-dose on Day 1: Initial dose followed by supplemental half-dose given 1.5-2.0 hours later. On Day 30 and Day 60, additional single-doses on the same schedule may be given if warranted.
Exposures Achieved at Maximum Tested Dose	Single Dose	Initial dose 150 mg (N=2) [24]: **MDMA** C_{max}: 441.9-486.9 ng/mL AUC_{0-24}: 5132.8-5232.0 ng*h/mL **MDA** C_{max}: 34.2-31.4 ng/mL AUC_{0-24}: 373.9-590.0 ng*h/mL
	Multiple Dose	Initial dose 50 mg + Supplemental dose 100 mg, 2.0 hours later (N=10) [260]: **MDMA** C_{max} +12.8%, AUC_{∞} +16.2% **MDA** C_{max}: +25%, AUC_{∞} +37.5% **HMMA** C_{max} -38.2%, AUC_{∞} -29.8%

Range of linear PK* **More PK data was available for 75 mg dose (N=8), which was used as basis for dose normalization* [24]	MDMA C_{max} normalized to 75 mg 100 mg (N=2): 1.53 125 mg (N=8): 1.81** 150 mg (N=2): 3.55 MDA C_{max} normalized to 75 mg 100 mg (N=2): 2.35 125 mg (N=8): 1.76 150 mg (N=2): 4.21 ** This ratio was confirmed in a more recent study with N=29 receiving 75 mg MDMA [542]. 125 mg (N=110): 1.83	MDMA AUC_{0-24} normalized to 75 mg 100 mg (N=2): 1.39 125 mg (N=8): 1.97 150 mg (N=2): 3.89 MDA AUC_{0-24} normalized to 75 mg 100 mg (N=2): 1.66 125 mg (N=8): 1.76 150 mg (N=2): 3.94
Accumulation at steady state	Therapeutic use is single-dose, MDMA does not reach steady state	
Metabolites	MDMA metabolism in the liver is saturable in a dose-dependent manner and follows non-linear pharmacokinetics. MDMA is metabolized by *N*-demethylation to the only active metabolite MDA by several enzymes, including CYP2D6 (>30%), CYP1A2, CYP3A4, CYP2C19, and CYP2B6, followed by COMT. The parent compound and MDA are further *O*-demethylated to HHMA and HHA, respectively. Both HHMA and HHA are subsequently *O*-methylated mainly to HMMA and HMA. These four metabolites, particularly HMMA and HMA, are excreted in the urine as conjugated glucuronide or sulfate metabolites.	
Absorption	Absolute/Relative Bioavailability	MDMA has not been studied with I.V. administration in humans to date.
	T_{max}	T_{max} by dose of MDMA administered [24]: · **Parent MDMA:** 75 mg: 1.8±0.4 hours 100 mg: 2-3 hours 125 mg: 2.4±1.0 hours 150 mg: 1.5-2 hours · **Active Metabolite MDA:** 75 mg: 5.1±2.6 hours 100 mg: 4-6 hours 125 mg: 7.1±2.8 hours 150 mg: 4-10 hours
Distribution	Vd/F or Vd	Vd/F by dose of MDMA administered [248]: 1.0 mg/kg MDMA (43-106 mg): 5.5±1.1 L/kg 1.6 mg/kg MDMA (69-150 mg): 5.5±1.3 L/kg
	% bound	34-40% Bound

Elimination	Route	· Primary route hepatic, 50% to 75% metabolized · Renal clearance 8% to 11% All metabolites of MDMA in urine were detected as glucuronide and sulfate conjugates. After 1.0 mg/kg MDMA, the majority was excreted in urine as the inactive metabolites HMMA sulfate (13%), followed by DHMA 3-sulfate (9%), and HMMA glucuronide (5%), and only 8% as the parent compound MDMA [248]. After 1.6 mg/kg MDMA, the majority was excreted in urine as the inactive metabolites HMMA sulfate (10%), followed by DHMA 3-sulfate (9%), and HMMA glucuronide (4%), and only 11% as the parent compound MDMA. Studies examining metabolism of 100 mg MDMA reported similar excretion values [248].
	Terminal $t_{½}$	Terminal $t_{1/2}$ by dose of MDMA administered [248]: · **Parent MDMA:** 1.0 mg/kg (43 mg-106 mg): 6.9±3.4 h 1.6 mg/kg (69 mg-150 mg): 8.1±2.1 h · **Active Metabolite MDA:** 1.0 mg/kg (43 mg-106 mg): 10.6±4.3 h 1.6 mg/kg (69 mg-150 mg): 12.3±3.7 h
	CL/F or CL	Renal CL by dose of MDMA administered [24]: 75 mg: 12.8±5.6 L/h 100 mg: 20.4-12.3 L/h 125 mg: 13.0±5.4 L/h 150 mg: 5.2-11.3 L/h CL/F by dose of MDMA administered [248]: 1.0 mg/kg (43 mg-106 mg): 0.62±0.19 L/h/kg 1.6 mg/kg (69 mg-150 mg): 0.48±0.11 L/h/kg
Intrinsic Factors	Age	Pediatric PK will be tested after initial NDA No information is available on effect of age on exposure, but from a mechanistic point of view, the enzymes responsible for metabolism of MDMA are not known to be affected by age.

	Sex	PK parameters by dose of MDMA administered [542]: **75 mg MDMA** MDMA C_{max}: Women 133±27 ng/mL MDMA C_{max}: Men 116±29 ng/mL MDMA AUC: Women 547±127 ng*h/mL MDMA AUC: Men 493±113 ng*h/mL **125 mg MDMA** MDMA C_{max}: Women 252±40 ng/mL MDMA C_{max}: Men 195±37 ng/mL MDMA AUC: Women 1058±185 ng*h/mL MDMA AUC: Men 838±160 ng*h/mL
	Race	PK parameters by dose of MDMA administered [248]: 1.0 mg/kg (43 mg-106 mg) MDMA: MDMA C_{max}: +22% in Blacks vs. Europeans MDMA AUC: +19% in Blacks vs. Europeans MDA C_{max}: +9.3% in Blacks vs. Europeans 1.6 mg/kg (69-150 mg) MDMA: MDMA C_{max}: +21% in Blacks vs. Europeans MDMA AUC: +8% in Blacks vs. Europeans MDA C_{max}: +1.4% in Blacks vs. Europeans
	Hepatic & Renal Impairment	CYP2D6 poor vs. extensive metabolizers [568]: MDMA C_{max} +15% MDA C_{max} +50% HMMA C_{max} -50-70% A PK study in subjects with moderate hepatic impairment is planned concurrent with Phase 3 studies. Due to<20% renal clearance of the parent compound, a renal impairment PK study is not planned to support the initial NDA.

Extrinsic Factors	Drug interactions	Paroxetine (N=7), CYP2D6 inhibitor, metabolized by CYP2D6>>CYP3A4>CYP1A2>CYP2C19>CYP3A5 [573]. **MDMA** C_{max} +17% AUC_{0-27} +23% **MDA** C_{max} +17% AUC_{0-27} +16% Bupropion (N=16) CYP2D6 and CYP2B6 inhibitor, metabolize [574]. **MDMA** C_{max} +14% AUC_{0-24} +33% $t_{1/2}$ +24% **MDA** C_{max} -15% AUC_{0-24} -12% 30 mg Dextromethorphan (N=12), metabolized by CYP2D6>> CYP3A4> CYP2B6. Co-administered with 1.5 mg/kg MDMA [552]. **Dextromethorphan** C_{max} +87.9% AUC_{0-8} +89.1% **Dextrorphan** C_{max} -93.0% AUC_{0-8} -90.4% **3-methoximorphinan** C_{max} +72.2% AUC_{0-8} +64.6% **Hydroxymorphinan-3-ol**

		C_{max} -87.2% AUC_{0-8} -86.7% Methylphenidate (N=16), metabolized by CYP2D6 [541] **MDMA** C_{max} -3.5% AUC_{0-24} +3.2% **MDA** C_{max} -3.6% AUC_{0-24} -3.4% **Methylphenidate** C_{max} +<0.1% AUC_{0-24} -<0.1%
	Food Effects	Will be tested concurrent with Phase 3

Expected High Clinical Exposure Scenario	Metabolism of MDMA is complex, with 50-75% of the parent compound being metabolized. Major enzymes involved in metabolism of MDMA include: CYP2D6 (>30%)> CYP1A2>CYP3A4>CYP2C19> CYP2B6. Active doses of MDMA (75 mg -125 mg) reversibly inhibit CYP2D6 and decrease CYP3A4 activity, with CYP2D6 activity normalizing after 10 days post-drug. Compensatory metabolic mechanisms have been demonstrated when CYP2D6 is inhibited, such as an increase in CYP1A2 activity by 20-40% [553]. In the therapeutic dose range of 75-125 mg, a concentration-dependent effect is observed. Studying higher doses of MDMA in healthy subjects poses both safety and ethical concerns due to the Schedule 1 controlled substance status of MDMA. Although elevation of blood pressure and heart rate has been observed, these cases have not been accompanied by clinical signs and symptoms of end organ effects of hypertension (e.g., chest pain, shortness of breath, neurological deficit or confusion) and have not been considered clinically significant AEs. The worst-case scenario would be strong inhibition of both CYP2D6, CYP2B6, and CYP1A2 combined with administration of an initial dose of 125 mg followed by a supplemental half-dose 1.5-2.0 hours later. Based on the exposure observed with CYP2D6/CYP2B6 inhibition by Bupropion with a C_{max} elevation of +14% and AUC elevation of +33%, combined with a C_{max} elevation of +12.8% and AUC elevation of +16.2% with a supplemental dose, the increase in exposure is estimated to be C_{max} +26.8% of MDMA and AUC +49.2% of MDMA. If CYP1A2 is additionally inhibited, a conservative estimate would be to double the exposure estimate for a C_{max} elevation of +53% and AUC could be elevated up to +75%. 125 mg: If an estimated 60% of metabolism is shut down, moderate hepatic impairment would double the AUC to be equivalent to 250 mg MDMA. PK exposure to single-doses above 150 mg MDMA remain untested to date. PK studies planned to be conducted concurrent with Phase 3 will cover a supra-therapeutic dose of 225 mg, which is sufficient close to 250 mg MDMA. In MAPS-sponsored clinical trials, MDMA is only administered under the supervision trained and qualified healthcare professionals in a controlled clinic setting.

Preclinical Cardiac Safety	**In vitro nonclinical data:** Langendorff perfused hearts isolated from male Sprague Dawley rats were used to explore in vitro effects of MDMA on QT interval. Solutions of MDMA (1, 3, 10 and 30 μM) were prepared by dissolving in Krebs-Henseleit buffer. After equilibration of the isolated rat heart, MDMA (1, 3, 10 and 30 μM) was added to the perfusate, with each concentration being allowed to perfuse for 15 minutes before being replaced with the next highest concentration. ECG and heart rate were continuously monitored using a Powerlab collation unit (Powerlab and Chart program V5, AD Instruments). Detection of P, QRS and T waves from the ECG waveform was facilitated with the Signal Averaged Electrocardiogram (SAECG) extension for Chart 5. Briefly, ECG cycles over 15-second sampling periods within each 15-minutes block were aligned and averaged. This ensured that random noise and signal uncorrelated with the ECG tended to cancel out, leaving the ECG components themselves unaffected. Heart rate was calculated from the R-R interval of the ECG waveform. ANOVA of the PQ, QRS interval, and T wave amplitude T(h) showed no effect of MDMA. ANOVA of the QT interval showed an effect of MDMA [$F(5,50)=5.22$, $p<0.01$]. Post-hoc comparisons did not reveal a significant effect of MDMA when compared to baseline (80±9 ms), although a trend towards an increase in the QT interval was observed following application of 30 μM MDMA in vehicle-treated (100±6 ms) groups. In addition, MDMA did not influence P wave, R or ST segment heights of the ECG trace (N=6 animals per group). Although a trend towards prolongation of the QT interval was observed with MDMA, it failed to reach significance. No increase in T wave amplitude of the ECG was observed with MDMA. These results support that the central and sympathomimetic effects of MDMA, rather than any direct action on cardiac tissue, are responsible for the sustained tachycardia observed in vivo [716]. **In vivo clinical data:** In an early clinical study [614] with 2-lead ECG monitoring during exposure to 1.5 mg/kg (71 mg-167 mg) MDMA, the mean change in QTc upon MDMA dosing relative to placebo was about 4.41 ms with an upper 95% confidence limit of 10.47 ms. The experimental design including the sample size, timing of the ECG measurements and type of ECG may not be optimal for precise assessment of QTc change. However, these data do support that the change in QTc, if any, is small and clinically unimportant. Despite a small sample size of N=24, the upper confidence limit is barely 10 msec. With more samples and 12-lead ECG, the upper confidence limit would likely be much less than 10 msec. See Type A Meeting Submission dated April 4, 2017 for methodology and individual data.

References

1. Mithoefer, M.C., et al., *MDMA-assisted psychotherapy for treatment of PTSD: study design and rationale for phase 3 trials based on pooled analysis of six phase 2 randomized controlled trials.* Psychopharmacology (Berl), 2019. **236**(9): p. 2735-2745.
2. Mithoefer, M.C., et al., *3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: a randomised, double-blind, dose-response, phase 2 clinical trial.* Lancet Psychiatry, 2018. **5**(6): p. 486-497.
3. Mithoefer, M.C., et al., *The safety and efficacy of {+/-}3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study.* J Psychopharmacol, 2011. **25**(4): p. 439-52.
4. Mithoefer, M.C., et al., *Durability of improvement in post-traumatic stress disorder symptoms and absence of harmful effects or drug dependency after 3,4-methylenedioxymethamphetamine-assisted psychotherapy: a prospective long-term follow-up study.* J Psychopharmacol, 2013. **27**(1): p. 28-39.
5. Oehen, P., et al., *A randomized, controlled pilot study of MDMA (+/- 3,4-Methylenedioxymethamphetamine)-assisted psychotherapy for treatment of resistant, chronic Post-Traumatic Stress Disorder (PTSD).* J Psychopharmacol, 2013. **27**(1): p. 40-52.
6. Ot'alora, G.M., et al., *3,4-Methylenedioxymethamphetamine-assisted psychotherapy for treatment of chronic posttraumatic stress disorder: A randomized phase 2 controlled trial.* J Psychopharmacol, 2018. **32**(12): p. 1295-1307
7. Kilpatrick, D.G., et al., *National estimates of exposure to traumatic events and PTSD prevalence using DSM-IV and DSM-5 criteria.* J Trauma Stress, 2013. **26**(5): p. 537-47.
8. Koenen, K.C., et al., *Posttraumatic stress disorder in the World Mental Health Surveys.* Psychol Med, 2017. **47**(13): p. 2260-2274.
9. Dorrington, S., et al., *Trauma, post-traumatic stress disorder and psychiatric disorders in a middle-income setting: prevalence and comorbidity.* Br J Psychiatry, 2014. **205**(5): p. 383-9.
10. Tarrier, N. and L. Gregg, *Suicide risk in civilian PTSD patients--predictors of suicidal ideation, planning and attempts.* Soc Psychiatry Psychiatr Epidemiol, 2004. **39**(8): p. 655-61.
11. Cipriani, A., et al., *Comparative efficacy and acceptability of pharmacological treatments for post-traumatic stress disorder in adults: a network meta-analysis.* Psychol Med, 2018. **48**(12): p. 1975-1984.
12. Lee, D.J., et al., *Psychotherapy Versus Pharmacotherapy for Posttraumatic Stress Disorder: Systemic Review and Meta-Analyses to Determine First-Line Treatments.* Depress Anxiety, 2016. **33**(9): p. 792-806.
13. Steenkamp, M.M., et al., *Psychotherapy for Military-Related PTSD: A Review of Randomized Clinical Trials.* JAMA, 2015. **314**(5): p. 489-500.
14. Bradley, R., et al., *A multidimensional meta-analysis of psychotherapy for PTSD.* Am J Psychiatry, 2005. **162**(2): p. 214-27.

15. Brady, K., et al., *Efficacy and safety of sertraline treatment of posttraumatic stress disorder: a randomized controlled trial.* JAMA, 2000. **283**(14): p. 1837-44.
16. Shulgin, A.T., *The background and chemistry of MDMA.* J Psychoactive Drugs, 1986. **18**(4): p. 291-304.
17. Kolbrich, E.A., et al., *Physiological and subjective responses to controlled oral 3,4-methylenedioxymethamphetamine administration.* J Clin Psychopharmacol, 2008. **28**(4): p. 432-40.
18. Cami, J., et al., *Human pharmacology of 3,4-methylenedioxymethamphetamine ("ecstasy"): psychomotor performance and subjective effects.* J Clin Psychopharmacol, 2000. **20**(4): p. 455-66.
19. Mas, M., et al., *Cardiovascular and neuroendocrine effects and pharmacokinetics of 3, 4-methylenedioxymethamphetamine in humans.* J Pharmacol Exp Ther, 1999. **290**(1): p. 136-45.
20. Harris, D.S., et al., *Subjective and hormonal effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans.* Psychopharmacology (Berl), 2002. **162**(4): p. 396-405.
21. Liechti, M.E., A. Gamma, and F.X. Vollenweider, *Gender differences in the subjective effects of MDMA.* Psychopharmacology (Berl), 2001. **154**(2): p. 161-8.
22. Tancer, M. and C.E. Johanson, *Reinforcing, subjective, and physiological effects of MDMA in humans: a comparison with d-amphetamine and mCPP.* Drug Alcohol Depend, 2003. **72**(1): p. 33-44.
23. Vollenweider, F.X., et al., *Psychological and cardiovascular effects and short-term sequelae of MDMA ("ecstasy") in MDMA-naive healthy volunteers.* Neuropsychopharmacology, 1998. **19**(4): p. 241-51.
24. de la Torre, R., et al., *Non-linear pharmacokinetics of MDMA ('ecstasy') in humans.* Br J Clin Pharmacol, 2000. **49**(2): p. 104-9.
25. Marks, D.M., C.U. Pae, and A.A. Patkar, *Triple reuptake inhibitors: a premise and promise.* Psychiatry Investig, 2008. **5**(3): p. 142-7.
26. Millan, M.J., *Dual- and triple-acting agents for treating core and co-morbid symptoms of major depression: novel concepts, new drugs.* Neurotherapeutics, 2009. **6**(1): p. 53-77.
27. Han, D.D. and H.H. Gu, *Comparison of the monoamine transporters from human and mouse in their sensitivities to psychostimulant drugs.* BMC Pharmacol, 2006. **6**: p. 6.
28. Liechti, M.E. and F.X. Vollenweider, *Which neuroreceptors mediate the subjective effects of MDMA in humans? A summary of mechanistic studies.* Hum Psychopharmacol, 2001. **16**(8): p. 589-598.
29. Murnane, K.S., et al., *Endocrine and neurochemical effects of 3,4-methylenedioxymethamphetamine and its stereoisomers in rhesus monkeys.* J Pharmacol Exp Ther, 2010. **334**(2): p. 642-50.
30. Setola, V., et al., *3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") induces fenfluramine-like proliferative actions on human cardiac valvular interstitial cells in vitro.* Mol Pharmacol, 2003. **63**(6): p. 1223-9.
31. Simmler, L.D., et al., *Monoamine transporter and receptor interaction profiles of a new series of designer cathinones.* Neuropharmacology, 2014. **79**: p. 152-60.
32. Carhart-Harris, R.L., et al., *The effect of acutely administered MDMA on subjective and BOLD-fMRI responses to favourite and worst autobiographical memories.* Int J Neuropsychopharmacol, 2014. **17**(4): p. 527-40.

33. Bedi, G., et al., *A window into the intoxicated mind? Speech as an index of psychoactive drug effects.* Neuropsychopharmacology, 2014. **39**(10): p. 2340-8.
34. Wardle, M.C., M.G. Kirkpatrick, and H. de Wit, *'Ecstasy' as a social drug: MDMA preferentially affects responses to emotional stimuli with social content.* Soc Cogn Affect Neurosci, 2014. **9**(8): p. 1076-81.
35. Wardle, M.C. and H. de Wit, *MDMA alters emotional processing and facilitates positive social interaction.* Psychopharmacology (Berl), 2014. **231**(21): p. 4219-29.
36. Wagner, A.C., et al., *Combining Cognitive-Behavioral Conjoint Therapy for PTSD with 3,4-Methylenedioxymethamphetamine (MDMA): A Case Example.* J Psychoactive Drugs, 2019: p. 1-8.
37. Danforth, A., *Findings from a collective case study of the MDMA/Ecstasy experiences of adults on the autism spectrum: Transcripts from Psychedelic Science 2013.* MAPS Bulletin, 2013. **23**(3): p. 30-35.
38. Danforth, A.L., *Embracing Neurodiversity in Psychedelic Science: A Mixed-Methods Inquiry into the MDMA Experiences of Autistic Adults.* J Psychoactive Drugs, 2019: p. 1-9.
39. Downing, J., *The psychological and physiological effects of MDMA on normal volunteers.* J Psychoactive Drugs, 1986. **18**(4): p. 335-40.
40. Lester, S.J., et al., *Cardiovascular effects of 3,4-methylenedioxymethamphetamine. A double-blind, placebo-controlled trial.* Ann Intern Med, 2000. **133**(12): p. 969-73.
41. Bedi, G., et al., *Effects of MDMA on sociability and neural response to social threat and social reward.* Psychopharmacology (Berl), 2009. **207**(1): p. 73-83.
42. Kirkpatrick, M.G., et al., *A direct comparison of the behavioral and physiological effects of methamphetamine and 3,4-methylenedioxymethamphetamine (MDMA) in humans.* Psychopharmacology (Berl), 2012. **219**(1): p. 109-22.
43. Grob, C., *MDMA research: preliminary investigations with human subjects.* Int J Drug Policy, 1998. **9**(2): p. 119-124.
44. Grob, C.S., et al., *Psychobiologic effects of 3,4-methylenedioxymethamphetamine in humans: methodological considerations and preliminary observations.* Behav Brain Res, 1996. **73**(1-2): p. 103-7.
45. Baggott, M.J., et al., *MDMA Impairs Response to Water Intake in Healthy Volunteers.* Adv Pharmacol Sci, 2016. **2016**: p. 2175896.
46. Pacifici, R., et al., *[Immunomodulator properties of ecstasy (MDMA)].* Ann Ist Super Sanita, 2000. **36**(1): p. 69-75.
47. Jerome, L., et al., *Long-term follow-up outcomes of MDMA-assisted psychotherapy for treatment of PTSD: a longitudinal pooled analysis of six phase 2 trials.* Psychopharmacology (Berl), 2020.
48. Freudenmann, R.W., F. Oxler, and S. Bernschneider-Reif, *The origin of MDMA (ecstasy) revisited: the true story reconstructed from the original documents.* Addiction, 2006. **101**(9): p. 1241-5.
49. Shulgin, A. and A. Shulgin, *Pihkal: A Chemical Love Story*. 1st ed. 1991, Berkeley, CA: Transform Press. 1-978.
50. Anderson, G.M.d., et al., *Absolute configuration and psychotomimetic activity.* NIDA Res Monogr, 1978. **22**: p. 8-15.

51. Shulgin, A.T. and D.E. Nichols, *Characterization of three new psychotomimetics*, in *The Pharmacology of Hallucinogens*, R.C. Stillman and R.E. Willette, Editors. 1978, Pergamon: New York.
52. Rudnick, G. and S.C. Wall, *The molecular mechanism of "ecstasy" [3,4-methylenedioxy-methamphetamine (MDMA)]: serotonin transporters are targets for MDMA-induced serotonin release.* Proc Natl Acad Sci U S A, 1992. **89**(5): p. 1817-21.
53. O'Neil, M.J., *The Merck Index: An Encyclopedia of chemicals, drugs and biologicals. Merck Research Laboratories, Merck and Co.* Inc, Whitehouse station, New Jersey, 2006. **319**.
54. Greer, G. and R. Tolbert, *Subjective reports of the effects of MDMA in a clinical setting.* J Psychoactive Drugs, 1986. **18**(4): p. 319-27.
55. Hysek, C.M., et al., *MDMA enhances emotional empathy and prosocial behavior.* Soc Cogn Affect Neurosci, 2014. **9**(11): p. 1645-52.
56. Kirkpatrick, M.G., et al., *Effects of MDMA and Intranasal oxytocin on social and emotional processing.* Neuropsychopharmacology, 2014. **39**(7): p. 1654-63.
57. Adamson, S., *Through the gateway of the heart: Accounts of experiences With MDMA and other empathogenic substances*. 1985, San Francisco CA: Four Trees Publications.
58. Grinspoon, L. and J.B. Bakalar, *Can drugs be used to enhance the psychotherapeutic process?* Am J Psychother, 1986. **40**(3): p. 393-404.
59. Nichols, D.E., *Differences between the mechanism of action of MDMA, MBDB, and the classic hallucinogens. Identification of a new therapeutic class: entactogens.* J Psychoactive Drugs, 1986. **18**(4): p. 305-13.
60. Greer, G. and R.J. Strassman, *Information on "Ecstasy".* Am J Psychiatry, 1985. **142**(11): p. 1391.
61. Greer, G.R. and R. Tolbert, *A method of conducting therapeutic sessions with MDMA.* J Psychoactive Drugs, 1998. **30**(4): p. 371-379.
62. Metzner, R. and S. Adamson, *Using MDMA in healing, psychotherapy and spiritual practice*, in *Ecstasy, A Complete Guide: A Comprehensive Look at the Risks and Benefits of MDMA.*, J. Holland, Editor. 2001, Inner Traditions: Rochester VT. p. 182-207.
63. Greer, G. and R. Tolbert, *The therapeutic use of MDMA.*, in *Ecstasy: The clinical, pharmacological and neurotoxicological effects of the drug MDMA.*, S.J. Peroutka, Editor. 1990, Kluver Academic: Boston, MA. p. 21-35.
64. Beck, J. and M. Rosenbaum, *Pursuit of Ecstasy: The MDMA Experience*. 1994, Albany, NY: SUNY Press.
65. US Department of Health and Human Services, S.A.a.M.H.S.A., Center for Behavioral Health Statistics and Quality, *National Survey on Drug Use and Health (NSDUH-2016-DS0001)*. 2018: Retrieved from https://datafiles.samhsa.gov/.
66. Europol, E.M.C.f.D.a.D.A.a., *EU Drug Markets Report 2019*. 2019, Publications Office of the European Union: Luxenbourg.
67. Drug Enforcement Agency, *Scheduling of Controlled Substances: Scheduling of 3,4-methylenedioxymethamphetamine (MDMA) into Schedule 1 of the Controlled Substances Act: Remand*, DEA, Editor. 1988, Federal Register: Washington, DC. p. 5156-5160.

68. Lawn, J.C., *On the Matter of MDMA Scheduling*, in *Docket No. 84-48*, Drug_Enforcement_Administration, Editor. 1986: Washington, DC.
69. Henry, J.A., K.J. Jeffreys, and S. Dawling, *Toxicity and deaths from 3,4-methylenedioxymethamphetamine ("ecstasy").* Lancet, 1992. **340**(8816): p. 384-7.
70. Cohen, R.S. and J. Cocores, *Neuropsychiatric manifestations following the use of 3,4-methylenedioxymethamphetamine (MDMA: "Ecstasy").* Prog Neuropsychopharmacol Biol Psychiatry, 1997. **21**(4): p. 727-34.
71. Williamson, S., et al., *Adverse effects of stimulant drugs in a community sample of drug users.* Drug Alcohol Depend, 1997. **44**(2-3): p. 87-94.
72. Krystal, J.H., et al., *Chronic 3,4-methylenedioxymethamphetamine (MDMA) use: effects on mood and neuropsychological function?* Am J Drug Alcohol Abuse, 1992. **18**(3): p. 331-41.
73. McCann, U.D., et al., *Serotonin neurotoxicity after (+/-)3,4-methylenedioxymethamphetamine (MDMA; "Ecstasy"): a controlled study in humans.* Neuropsychopharmacology, 1994. **10**(2): p. 129-38.
74. McCann, U.D., et al., *Cognitive performance in (+/-) 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") users: a controlled study.* Psychopharmacology (Berl), 1999. **143**(4): p. 417-25.
75. Parrott, A.C. and J. Lasky, *Ecstasy (MDMA) effects upon mood and cognition: before, during and after a Saturday night dance.* Psychopharmacology (Berl), 1998. **139**(3): p. 261-8.
76. Ricaurte, G.A., et al., *Toxicodynamics and long-term toxicity of the recreational drug, 3, 4-methylenedioxymethamphetamine (MDMA, 'Ecstasy').* Toxicol Lett, 2000. **112-113**: p. 143-6.
77. Baumann, M.H., et al., *Effects of dose and route of administration on pharmacokinetics of (+ or -)-3,4-methylenedioxymethamphetamine in the rat.* Drug Metab Dispos, 2009. **37**(11): p. 2163-70.
78. Biezonski, D.K. and J.S. Meyer, *The Nature of 3, 4-Methylenedioxymethamphetamine (MDMA)-Induced Serotonergic Dysfunction: Evidence for and Against the Neurodegeneration Hypothesis.* Curr Neuropharmacol, 2011. **9**(1): p. 84-90.
79. Gouzoulis-Mayfrank, E. and J. Daumann, *The confounding problem of polydrug use in recreational ecstasy/MDMA users: a brief overview.* J Psychopharmacol, 2006. **20**(2): p. 188-93.
80. Rogers, G., et al., *The harmful health effects of recreational ecstasy: a systematic review of observational evidence.* Health Technol Assess, 2009. **13**(6): p. iii-iv, ix-xii, 1-315.
81. Bouso, J.C., et al., *MDMA-assisted psychotherapy using low doses in a small sample of women with chronic posttraumatic stress disorder.* J Psychoactive Drugs, 2008. **40**(3): p. 225-36.
82. Bedi, G., D. Hyman, and H. de Wit, *Is ecstasy an "empathogen"? Effects of +/-3,4-methylenedioxymethamphetamine on prosocial feelings and identification of emotional states in others.* Biol Psychiatry, 2010. **68**(12): p. 1134-40.
83. Dumont, G.J., et al., *Increased oxytocin concentrations and prosocial feelings in humans after ecstasy (3,4-methylenedioxymethamphetamine) administration.* Soc Neurosci, 2009. **4**(4): p. 359-66.

84. Farre, M., et al., *Pharmacological interaction between 3,4-methylenedioxymethamphetamine (ecstasy) and paroxetine: pharmacological effects and pharmacokinetics.* J Pharmacol Exp Ther, 2007. **323**(3): p. 954-62.
85. Hysek, C.M., G. Domes, and M.E. Liechti, *MDMA enhances "mind reading" of positive emotions and impairs "mind reading" of negative emotions.* Psychopharmacology (Berl), 2012. **222**(2): p. 293-302.
86. van Wel, J.H., et al., *Effects of Acute MDMA Intoxication on Mood and Impulsivity: Role of the 5-HT(2) and 5-HT(1) Receptors.* PLoS One, 2012. **7**(7): p. e40187.
87. Feduccia, A.A., J. Holland, and M.C. Mithoefer, *Progress and promise for the MDMA drug development program.* Psychopharmacology (Berl), 2018. **235**(2): p. 561-571.
88. Lyon, R.A., R.A. Glennon, and M. Titeler, *3,4-Methylenedioxymethamphetamine (MDMA): stereoselective interactions at brain 5-HT1 and 5-HT2 receptors.* Psychopharmacology (Berl), 1986. **88**(4): p. 525-6.
89. Navarro, M., et al., *Usefulness of saliva for measurement of 3,4-methylenedioxymethamphetamine and its metabolites: correlation with plasma drug concentrations and effect of salivary pH.* Clin Chem, 2001. **47**(10): p. 1788-95.
90. Kousik, S.M., T.C. Napier, and P.M. Carvey, *The effects of psychostimulant drugs on blood brain barrier function and neuroinflammation.* Front Pharmacol, 2012. **3**: p. 121.
91. Hardman, H.F., C.O. Haavik, and M.H. Seevers, *Relationship of the structure of mescaline and seven analogs to toxicity and behavior in five species of laboratory animals.* Toxicol Appl Pharmacol, 1973. **25**(2): p. 299-309.
92. Gardani, M., R.N. Blance, and S.M. Biello, *MDMA alters the response of the mammalian circadian clock in hamsters: effects on re-entrainment and triazolam-induced phase shifts.* Brain Res, 2005. **1046**(1-2): p. 105-15.
93. Mechan, A., et al., *Pharmacokinetic profile of single and repeated oral doses of MDMA in squirrel monkeys: relationship to lasting effects on brain serotonin neurons.* Neuropsychopharmacology, 2006. **31**(2): p. 339-50.
94. Wang, X., et al., *(+/-)-3,4-Methylenedioxymethamphetamine administration to rats does not decrease levels of the serotonin transporter protein or alter its distribution between endosomes and the plasma membrane.* J Pharmacol Exp Ther, 2005. **314**(3): p. 1002-12.
95. Frith, C.H., et al., *Toxicity of methylenedioxymethamphetamine (MDMA) in the dog and the rat.* Fundam Appl Toxicol, 1987. **9**(1): p. 110-9.
96. Frith, C.H. and W. Slikker, *28-Day Oral Toxicity of Methylenedioxymethamphetamine hydrochloride in rats: Protocol # EMD-SC-002.* 1985, MAPS: Unpublished.
97. Johnson, M.P., A.J. Hoffman, and D.E. Nichols, *Effects of the enantiomers of MDA, MDMA and related analogues on [3H]serotonin and [3H]dopamine release from superfused rat brain slices.* Eur J Pharmacol, 1986. **132**(2-3): p. 269-76.
98. Cole, J.C. and H.R. Sumnall, *The pre-clinical behavioural pharmacology of 3,4-methylenedioxymethamphetamine (MDMA).* Neurosci Biobehav Rev, 2003. **27**(3): p. 199-217.

99. Zsilla, G., et al., *3,4-Methylenedioxymethamphetamine, mephedrone, and beta-phenylethylamine release dopamine from the cytoplasm by means of transporters and keep the concentration high and constant by blocking reuptake.* Eur J Pharmacol, 2018. **837**: p. 72-80.
100. Fitzgerald, J.L. and J.J. Reid, *Effects of methylenedioxymethamphetamine on the release of monoamines from rat brain slices.* Eur J Pharmacol, 1990. **191**(2): p. 217-20.
101. Kankaanpaa, A., et al., *The acute effects of amphetamine derivatives on extracellular serotonin and dopamine levels in rat nucleus accumbens.* Pharmacol Biochem Behav, 1998. **59**(4): p. 1003-9.
102. Verrico, C.D., G.M. Miller, and B.K. Madras, *MDMA (Ecstasy) and human dopamine, norepinephrine, and serotonin transporters: implications for MDMA-induced neurotoxicity and treatment.* Psychopharmacology (Berl), 2007. **189**(4): p. 489-503.
103. Cozzi, N.V., et al., *Inhibition of plasma membrane monoamine transporters by beta-ketoamphetamines.* Eur J Pharmacol, 1999. **381**(1): p. 63-9.
104. Partilla, J.S., et al., *Interaction of amphetamines and related compounds at the vesicular monoamine transporter.* J Pharmacol Exp Ther, 2006. **319**(1): p. 237-46.
105. Bogen, I.L., et al., *Short- and long-term effects of MDMA ("ecstasy") on synaptosomal and vesicular uptake of neurotransmitters in vitro and ex vivo.* Neurochem Int, 2003. **43**(4-5): p. 393-400.
106. Gu, X.F. and E.C. Azmitia, *Integrative transporter-mediated release from cytoplasmic and vesicular 5-hydroxytryptamine stores in cultured neurons.* Eur J Pharmacol, 1993. **235**(1): p. 51-7.
107. Leonardi, E.T. and E.C. Azmitia, *MDMA (ecstasy) inhibition of MAO type A and type B: comparisons with fenfluramine and fluoxetine (Prozac).* Neuropsychopharmacology, 1994. **10**(4): p. 231-8.
108. Pilgrim, J.L., et al., *Serotonin toxicity involving MDMA (ecstasy) and moclobemide.* Forensic Sci Int, 2012. **215**(1-3): p. 184-8.
109. Vuori, E., et al., *Death following ingestion of MDMA (ecstasy) and moclobemide.* Addiction, 2003. **98**(3): p. 365-8.
110. Slikker, W., Jr., et al., *Behavioral and neurochemical effects of orally administered MDMA in the rodent and nonhuman primate.* Neurotoxicology, 1989. **10**(3): p. 529-42.
111. Mlinar, B. and R. Corradetti, *Endogenous 5-HT, released by MDMA through serotonin transporter- and secretory vesicle-dependent mechanisms, reduces hippocampal excitatory synaptic transmission by preferential activation of 5-HT1B receptors located on CA1 pyramidal neurons.* Eur J Neurosci, 2003. **18**(6): p. 1559-71.
112. Rothman, R.B. and M.H. Baumann, *Monoamine transporters and psychostimulant drugs.* Eur J Pharmacol, 2003. **479**(1-3): p. 23-40.
113. Gudelsky, G.A. and B.K. Yamamoto, *Actions of 3,4-methylenedioxymethamphetamine (MDMA) on cerebral dopaminergic, serotonergic and cholinergic neurons.* Pharmacol Biochem Behav, 2008. **90**(2): p. 198-207.

114. Feduccia, A.A., N. Kongovi, and C.L. Duvauchelle, *Heat increases MDMA-enhanced NAcc 5-HT and body temperature, but not MDMA self-administration.* Eur Neuropsychopharmacol, 2010. **20**(12): p. 884-94.
115. Yamamoto, B.K. and L.J. Spanos, *The acute effects of methylenedioxymethamphetamine on dopamine release in the awake-behaving rat.* Eur J Pharmacol, 1988. **148**(2): p. 195-203.
116. Shankaran, M. and G.A. Gudelsky, *Effect of 3,4-methylenedioxymethamphetamine (MDMA) on hippocampal dopamine and serotonin.* Pharmacol Biochem Behav, 1998. **61**(4): p. 361-6.
117. Bradbury, S., et al., *Acquisition of MDMA self-administration: pharmacokinetic factors and MDMA-induced serotonin release.* Addict Biol, 2014. **19**(5): p. 874-84.
118. Lazenka, M.F., et al., *Sex differences in abuse-related neurochemical and behavioral effects of 3,4-methylenedioxymethamphetamine (MDMA) in rats.* Pharmacol Biochem Behav, 2017. **152**: p. 52-60.
119. Acquas, E., et al., *Intravenous administration of ecstasy (3,4-methylendioxymethamphetamine) enhances cortical and striatal acetylcholine release in vivo.* Eur J Pharmacol, 2001. **418**(3): p. 207-11.
120. Nair, S.G. and G.A. Gudelsky, *3,4-Methylenedioxymethamphetamine enhances the release of acetylcholine in the prefrontal cortex and dorsal hippocampus of the rat.* Psychopharmacology (Berl), 2006. **184**(2): p. 182-9.
121. Battaglia, G., et al., *Pharmacologic profile of MDMA (3,4-methylenedioxymethamphetamine) at various brain recognition sites.* Eur J Pharmacol, 1988. **149**(1-2): p. 159-63.
122. Jones, D.C., S.S. Lau, and T.J. Monks, *Thioether metabolites of 3,4-methylenedioxyamphetamine and 3,4-methylenedioxymethamphetamine inhibit human serotonin transporter (hSERT) function and simultaneously stimulate dopamine uptake into hSERT-expressing SK-N-MC cells.* J Pharmacol Exp Ther, 2004. **311**(1): p. 298-306.
123. PDSP, *MDMA receptor binding profiles from Psychoactive Drug Screening Program Database Contract # NO1MH32004 (NIMH PDSP), with data accessed between November 12 and November 14, 2007.* 2007, National Institute of Mental Health.
124. Giannaccini, G., et al., *Short-term effects of 3,4-methylen-dioxy-metamphetamine (MDMA) on 5-HT(1A) receptors in the rat hippocampus.* Neurochem Int, 2007. **51**(8): p. 496-506.
125. Brunner, D. and R. Hen, *Insights into the neurobiology of impulsive behavior from serotonin receptor knockout mice.* Ann N Y Acad Sci, 1997. **836**: p. 81-105.
126. Graeff, F.G., et al., *Role of 5-HT in stress, anxiety, and depression.* Pharmacol Biochem Behav, 1996. **54**(1): p. 129-41.
127. Glennon, R.A. and R. Young, *MDMA stimulus generalization to the 5-HT(1A) serotonin agonist 8-hydroxy-2- (di-n-propylamino)tetralin.* 2000. **66**(3): p. 483-488.
128. Glennon, R.A., et al., *N-Methyl-1-(4-methoxyphenyl)-2-aminopropane (PMMA) and N-Methyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane (MDMA) produce non-identical discriminative stimuli in rats.* Pharmacol Biochem Behav, 2007. **86**(3): p. 477-84.

129. Schechter, M.D., *Discriminative profile of MDMA.* Pharmacol Biochem Behav, 1986. **24**(6): p. 1533-7.
130. Webster, J.I., D.N. Harper, and S. Schenk, *Generalization of serotonin and dopamine ligands to the discriminative stimulus effects of different doses of +/- 3,4-methylenedioxymethamphetamine.* Behav Pharmacol, 2017. **28**(4): p. 245-254.
131. Schenk, S. and Q. Highgate, *Dopamine and serotonin antagonists fail to alter the discriminative stimulus properties of +/-methylenedioxymethamphetamine.* Behav Pharmacol, 2019. **30**(4): p. 327-334.
132. Nair, S.G. and G.A. Gudelsky, *3,4-Methylenedioxymethamphetamine (MDMA) enhances the release of acetylcholine by 5-HT4 and D1 receptor mechanisms in the rat prefrontal cortex.* Synapse, 2005. **58**(4): p. 229-35.
133. Kuteykin-Teplyakov, K. and R. Maldonado, *Looking for prosocial genes: ITRAQ analysis of proteins involved in MDMA-induced sociability in mice.* Eur Neuropsychopharmacol, 2014. **24**(11): p. 1773-83.
134. Belmer, A., et al., *Positive regulation of raphe serotonin neurons by serotonin 2B receptors.* Neuropsychopharmacology, 2018. **43**(7): p. 1623-1632.
135. Bankson, M.G. and B.K. Yamamoto, *Serotonin-GABA interactions modulate MDMA-induced mesolimbic dopamine release.* J Neurochem, 2004. **91**(4): p. 852-9.
136. Cordero-Erausquin, M., et al., *Nicotinic receptor function: new perspectives from knockout mice.* Trends Pharmacol Sci, 2000. **21**(6): p. 211-7.
137. Llabres, S., et al., *Molecular basis of the selective binding of MDMA enantiomers to the alpha4beta2 nicotinic receptor subtype: synthesis, pharmacological evaluation and mechanistic studies.* Eur J Med Chem, 2014. **81**: p. 35-46.
138. Jorgensen, H., et al., *Serotonin receptors involved in vasopressin and oxytocin secretion.* J Neuroendocrinol, 2003. **15**(3): p. 242-9.
139. Forsling, M.L., et al., *The effect of 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy') and its metabolites on neurohypophysial hormone release from the isolated rat hypothalamus.* Br J Pharmacol, 2002. **135**(3): p. 649-56.
140. Thompson, M.R., et al., *A role for oxytocin and 5-HT(1A) receptors in the prosocial effects of 3,4 methylenedioxymethamphetamine ("ecstasy").* Neuroscience, 2007. **146**(2): p. 509-14.
141. Morley, K.C., J.C. Arnold, and I.S. McGregor, *Serotonin (1A) receptor involvement in acute 3,4-methylenedioxymethamphetamine (MDMA) facilitation of social interaction in the rat.* Prog Neuropsychopharmacol Biol Psychiatry, 2005. **29**(5): p. 648-57.
142. Broadbear, J.H., et al., *Oxytocinergic regulation of endogenous as well as drug-induced mood.* Pharmacol Biochem Behav, 2014. **119**: p. 61-71.
143. Pettie, M., et al., *A genetic deletion of the serotonin transporter differentially influences the behavioural effects of MDMA.* J Psychopharmacol, 2019. **33**(3): p. 355-363.
144. Ferraz de Paula, V., et al., *Methylenedioxymethamphetamine (Ecstasy) Decreases Neutrophil Activity and Alters Leukocyte Distribution in Bone Marrow, Spleen and Blood.* Neuroimmunomodulation, 2009. **16**(3): p. 191-200.
145. Nash, J.F., Jr., H.Y. Meltzer, and G.A. Gudelsky, *Elevation of serum prolactin and corticosterone concentrations in the rat after the administration of 3,4-methylenedioxymethamphetamine.* J Pharmacol Exp Ther, 1988. **245**(3): p. 873-9.

146. Connor, T.J., J.P. Kelly, and B.E. Leonard, *An assessment of the acute effects of the serotonin releasers methylenedioxymethamphetamine, methylenedioxyamphetamine and fenfluramine on immunity in rats.* Immunopharmacology, 2000. **46**(3): p. 223-35.
147. Murnane, K.S., et al., *The neuropharmacology of prolactin secretion elicited by 3,4-methylenedioxymethamphetamine ("ecstasy"): a concurrent microdialysis and plasma analysis study.* Horm Behav, 2012. **61**(2): p. 181-90.
148. Tiangco, D.A., et al., *3,4-Methylenedioxymethamphetamine activates nuclear factor-kappaB, increases intracellular calcium, and modulates gene transcription in rat heart cells.* Cardiovasc Toxicol, 2005. **5**(3): p. 301-10.
149. Schindler, C.W., et al., *Effects of 3,4-methylenedioxymethamphetamine (MDMA) and its main metabolites on cardiovascular function in conscious rats.* Br J Pharmacol, 2014. **171**(1): p. 83-91.
150. Fallon, J.K., et al., *Action of MDMA (ecstasy) and its metabolites on arginine vasopressin release.* Ann N Y Acad Sci, 2002. **965**: p. 399-409.
151. Fonsart, J., et al., *Sprague-Dawley rats display sex-linked differences in the pharmacokinetics of 3,4-methylenedioxymethamphetamine (MDMA) and its metabolite 3,4-methylenedioxyamphetamine (MDA).* Toxicol Appl Pharmacol, 2009. **241**(3): p. 339-47.
152. Malpass, A., et al., *Acute toxicity of 3,4-methylenedioxymethamphetamine (MDMA) in Sprague-Dawley and Dark Agouti rats.* Pharmacol Biochem Behav, 1999. **64**(1): p. 29-34.
153. Palenicek, T., et al., *Increased sensitivity to the acute effects of MDMA ("ecstasy") in female rats.* Physiol Behav, 2005. **86**(4): p. 546-53.
154. Davis, W.M., H.T. Hatoum, and I.W. Waters, *Toxicity of MDA (3,4-methylenedioxyamphetamine) considered for relevance to hazards of MDMA (Ecstasy) abuse.* Alcohol Drug Res, 1987. **7**(3): p. 123-34.
155. Fantegrossi, W.E., et al., *Pharmacological characterization of the effects of 3,4-methylenedioxymethamphetamine ("ecstasy") and its enantiomers on lethality, core temperature, and locomotor activity in singly housed and crowded mice.* Psychopharmacology (Berl), 2003. **166**(3): p. 202-11.
156. Mahmood, I. and J.D. Balian, *Interspecies scaling: a comparative study for the prediction of clearance and volume using two or more than two species.* Life Sci, 1996. **59**(7): p. 579-85.
157. Fantegrossi, W.E., et al., *Nantenine: an antagonist of the behavioral and physiological effects of MDMA in mice.* Psychopharmacology (Berl), 2004. **173**(3-4): p. 270-7.
158. Meyer, J.S., et al., *Neural effects of MDMA as determined by functional magnetic resonance imaging and magnetic resonance spectroscopy in awake marmoset monkeys.* Ann N Y Acad Sci, 2006. **1074**: p. 365-76.
159. Molliver, M.E., et al., *Neurotoxicity of MDMA and related compounds: anatomic studies.* Ann N Y Acad Sci, 1990. **600**: p. 649-61; discussion 661-4.
160. O'Callaghan, J.P. and D.B. Miller, *Neurotoxicity profiles of substituted amphetamines in the C57BL/6J mouse.* J Pharmacol Exp Ther, 1994. **270**(2): p. 741-51.
161. Sabol, K.E., et al., *Amphetamine analogs have differential effects on DRL 36-s schedule performance.* Psychopharmacology (Berl), 1995. **121**(1): p. 57-65.

162. Miller, D.B. and J.P. O'Callaghan, *Neurotoxicity of d-amphetamine in the C57BL/6J and CD-1 mouse. Interactions with stress and the adrenal system.* Ann N Y Acad Sci, 1996. **801**: p. 148-67.
163. Collins, S.A., G.A. Gudelsky, and B.K. Yamamoto, *MDMA-induced loss of parvalbumin interneurons within the dentate gyrus is mediated by 5HT2A and NMDA receptors.* Eur J Pharmacol, 2015. **761**: p. 95-100.
164. Ma, K.H., et al., *Effects of dextromethorphan on MDMA-induced serotonergic aberration in the brains of non-human primates using [(123)I]-ADAM/SPECT.* Sci Rep, 2016. **6**: p. 38695.
165. Karimi, S., M. Jahanshahi, and M.J. Golalipour, *The Effect of MDMA-Induced Anxiety on Neuronal Apoptosis in Adult Male Rats' Hippocampus.* Folia Biol (Praha), 2014. **60**(4): p. 187-91.
166. Isbister, G.K. and N.A. Buckley, *The pathophysiology of serotonin toxicity in animals and humans: implications for diagnosis and treatment.* Clin Neuropharmacol, 2005. **28**(5): p. 205-14.
167. Gillman, P.K., *Ecstasy, serotonin syndrome and the treatment of hyperpyrexia.* Med J Aust, 1997. **167**(2): p. 109, 111.
168. Mueller, P.D. and W.S. Korey, *Death by "ecstasy": the serotonin syndrome?* Ann Emerg Med, 1998. **32**(3 Pt 1): p. 377-80.
169. Dutta, R.R., M.A. Taffe, and C.D. Mandyam, *Chronic administration of amphetamines disturbs development of neural progenitor cells in young adult nonhuman primates.* Prog Neuropsychopharmacol Biol Psychiatry, 2018. **85**: p. 46-53.
170. Frith, C.H. and W. Slikker, *28-Day Oral Toxicity of Methylenedioxymethamphetamine hydrochloride in dogs: Protocol # EMD-SC-001*. 1985: Unpublished: MAPS [As Earth Metabolic Design Laboratories].
171. Selken, J. and D.E. Nichols, *Alpha1-adrenergic receptors mediate the locomotor response to systemic administration of (+/-)-3,4-methylenedioxymethamphetamine (MDMA) in rats.* Pharmacol Biochem Behav, 2007. **86**(4): p. 622-30.
172. Fletcher, P.J., J. Sinyard, and G.A. Higgins, *The effects of the 5-HT(2C) receptor antagonist SB242084 on locomotor activity induced by selective, or mixed, indirect serotonergic and dopaminergic agonists.* Psychopharmacology (Berl), 2006. **187**(4): p. 515-25.
173. Crean, R.D., et al., *Effects of (+/-)3,4-methylenedioxymethamphetamine, (+/-)3,4-methylenedioxyamphetamine and methamphetamine on temperature and activity in rhesus macaques.* Neuroscience, 2006. **142**(2): p. 515-25.
174. Bhattacharya, S.K., A. Bhattacharya, and S. Ghosal, *Anxiogenic activity of methylenedioxymethamphetamine (Ecstasy): an experimental study.* Biogenic Amines, 1998. **7**: p. 217-237.
175. Ho, Y.J., et al., *Acute and long-term consequences of single MDMA administration in relation to individual anxiety levels in the rat.* Behav Brain Res, 2004. **149**(2): p. 135-44.
176. Budzynska, B., et al., *Acute behavioral effects of co-administration of mephedrone and MDMA in mice.* Pharmacol Rep, 2017. **69**(2): p. 199-205.
177. Mechan, A.O., et al., *A study of the effect of a single neurotoxic dose of 3,4-methylenedioxymethamphetamine (MDMA; "ecstasy") on the subsequent long-*

term behaviour of rats in the plus maze and open field. Psychopharmacology (Berl), 2002. **159**(2): p. 167-75.
178. Gurtman, C.G., et al., *Increased anxiety in rats after 3,4-methylenedioxymethamphetamine: association with serotonin depletion.* Eur J Pharmacol, 2002. **446**(1-3): p. 89-96.
179. Clemens, K.J., et al., *MDMA ("ecstasy"), methamphetamine and their combination: long-term changes in social interaction and neurochemistry in the rat.* Psychopharmacology (Berl), 2004. **173**(3-4): p. 318-25.
180. Ando, R.D., et al., *Partial lesion of the serotonergic system by a single dose of MDMA results in behavioural disinhibition and enhances acute MDMA-induced social behaviour on the social interaction test.* Neuropharmacology, 2006. **50**(7): p. 884-96.
181. Garcia-Pardo, M.P., et al., *Cognitive and behavioural effects induced by social stress plus MDMA administration in mice.* Behav Brain Res, 2017. **319**: p. 63-72.
182. Thompson, M.R., G.E. Hunt, and I.S. McGregor, *Neural correlates of MDMA ("Ecstasy")-induced social interaction in rats.* Soc Neurosci, 2009. **4**(1): p. 60-72.
183. Hunt, G.E., et al., *MDMA-induced c-Fos expression in oxytocin-containing neurons is blocked by pretreatment with the 5-HT-1A receptor antagonist WAY 100635.* Brain Res Bull, 2011. **86**(1-2): p. 65-73.
184. Hasler, F., et al., *Investigation of serotonin-1A receptor function in the human psychopharmacology of MDMA.* J Psychopharmacol, 2009. **23**(8): p. 923-35.
185. Hysek, C.M., F.X. Vollenweider, and M.E. Liechti, *Effects of a beta-blocker on the cardiovascular response to MDMA (Ecstasy).* Emerg Med J, 2010. **27**(8): p. 586-9.
186. van Wel, J.H., et al., *Blockade of 5-HT(2) Receptor Selectively Prevents MDMA-Induced Verbal Memory Impairment.* Neuropsychopharmacology, 2011. **36**(9): p. 1932-9.
187. Liester, M.B., et al., *Phenomenology and sequelae of 3,4-methylenedioxymethamphetamine use.* J Nerv Ment Dis, 1992. **180**(6): p. 345-52; discussion 353-4.
188. Peroutka, S.J., H. Newman, and H. Harris, *Subjective effects of 3,4-methylenedioxymethamphetamine in recreational users.* Neuropsychopharmacology, 1988. **1**(4): p. 273-7.
189. Solowij, N., W. Hall, and N. Lee, *Recreational MDMA use in Sydney: a profile of 'Ecstacy' users and their experiences with the drug.* Br J Addict, 1992. **87**(8): p. 1161-72.
190. Pitts, E.G., et al., *3,4-Methylenedioxymethamphetamine Increases Affiliative Behaviors in Squirrel Monkeys in a Serotonin 2A Receptor-Dependent Manner.* Neuropsychopharmacology, 2017.
191. Edsinger, E. and G. Dolen, *A Conserved Role for Serotonergic Neurotransmission in Mediating Social Behavior in Octopus.* Curr Biol, 2018. **28**(19): p. 3136-3142 e4.
192. Stewart, A., et al., *Behavioral effects of MDMA ('ecstasy') on adult zebrafish.* Behav Pharmacol, 2011. **22**(3): p. 275-80.
193. Taffe, M.A., et al., *Functional consequences of repeated (+/-)3,4-methylenedioxymethamphetamine (MDMA) treatment in rhesus monkeys.* Neuropsychopharmacology, 2001. **24**(3): p. 230-9.

194. Goodwin, A.K. and L.E. Baker, *A three-choice discrimination procedure dissociates the discriminative stimulus effects of d-amphetamine and (+/-)-MDMA in rats.* Exp Clin Psychopharmacol, 2000. **8**(3): p. 415-23.
195. Goodwin, A.K., et al., *Behavioral effects and pharmacokinetics of (+/-)-3,4-methylenedioxymethamphetamine (MDMA, Ecstasy) after intragastric administration to baboons.* J Pharmacol Exp Ther, 2013. **345**(3): p. 342-53.
196. Plaza-Zabala, A., et al., *Effects of repeated MDMA administration on the motivation for palatable food and extinction of operant responding in mice.* Psychopharmacology (Berl), 2010. **208**(4): p. 563-73.
197. Mohr, D., et al., *Acute and long-term effect of MDMA on startle reflex and prepulse inhibition in rats.* Behav Pharmacol, 2007. **18**: p. S14-S14.
198. Arrue, A., F.M. Gomez, and M.T. Giralt, *Effects of 3,4-methylenedioxymethamphetamine ('Ecstasy') on the jaw-opening reflex and on the alpha-adrenoceptors which regulate this reflex in the anesthetized rat.* Eur J Oral Sci, 2004. **112**(2): p. 127-33.
199. Gordon, C.J., *Thermophysiological responses to hyperthermic drugs: extrapolating from rodent to human.* Prog Brain Res, 2007. **162**: p. 63-79.
200. Reveron, M.E., E.Y. Maier, and C.L. Duvauchelle, *Experience-dependent changes in temperature and behavioral activity induced by MDMA.* Physiol Behav, 2006. **89**(3): p. 358-63.
201. Concheiro, M., et al., *Nonlinear pharmacokinetics of (+/-)3,4-methylenedioxymethamphetamine (MDMA) and its pharmacodynamic consequences in the rat.* Drug Metab Dispos, 2014. **42**(1): p. 119-25.
202. Musolino, S.T., et al., *Improved method for optical fiber temperature probe implantation in brains of free-moving rats.* J Neurosci Methods, 2019. **313**: p. 24-28.
203. Kiyatkin, E.A., et al., *Critical role of peripheral vasoconstriction in fatal brain hyperthermia induced by MDMA (Ecstasy) under conditions that mimic human drug use.* J Neurosci, 2014. **34**(23): p. 7754-62.
204. Dafters, R.I., *Effect of ambient temperature on hyperthermia and hyperkinesis induced by 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy") in rats.* Psychopharmacology (Berl), 1994. **114**(3): p. 505-8.
205. Malberg, J.E. and L.S. Seiden, *Small changes in ambient temperature cause large changes in 3,4-methylenedioxymethamphetamine (MDMA)-induced serotonin neurotoxicity and core body temperature in the rat.* J Neurosci, 1998. **18**(13): p. 5086-94.
206. Feio-Azevedo, R., et al., *Aged rats are more vulnerable than adolescents to "ecstasy"-induced toxicity.* Arch Toxicol, 2018. **92**(7): p. 2275-2295.
207. Gordon, C.J., et al., *Effects of 3,4-methylenedioxymethamphetamine on autonomic thermoregulatory responses of the rat.* Pharmacol Biochem Behav, 1991. **38**(2): p. 339-44.
208. Pedersen, N.P. and W.W. Blessing, *Cutaneous vasoconstriction contributes to hyperthermia induced by 3,4-methylenedioxymethamphetamine (ecstasy) in conscious rabbits.* J Neurosci, 2001. **21**(21): p. 8648-54.
209. Von Huben, S.N., et al., *Impact of ambient temperature on hyperthermia induced by (+/-)3,4-methylenedioxymethamphetamine in rhesus macaques.* Neuropsychopharmacology, 2007. **32**(3): p. 673-81.

210. Bowyer, J.F., et al., *Plasma levels of parent compound and metabolites after doses of either d-fenfluramine or d-3,4-methylenedioxymethamphetamine (MDMA) that produce long-term serotonergic alterations.* Neurotoxicology, 2003. **24**(3): p. 379-90.
211. Freedman, R.R., C.E. Johanson, and M.E. Tancer, *Thermoregulatory effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans.* Psychopharmacology (Berl), 2005. **183**(2): p. 248-56.
212. Crean, R.D., S.A. Davis, and M.A. Taffe, *Oral administration of (+/-)3,4-methylenedioxymethamphetamine and (+)methamphetamine alters temperature and activity in rhesus macaques.* Pharmacol Biochem Behav, 2007. **87**(1): p. 11-9.
213. Banks, M.L., et al., *Ambient temperature effects on 3,4-methylenedioxymethamphetamine-induced thermodysregulation and pharmacokinetics in male monkeys.* Drug Metab Dispos, 2007. **35**(10): p. 1840-5.
214. De La Torre, R., et al., *Non-linear pharmacokinetics of MDMA ('ecstasy') in humans: Non-linear pharmacokinetics of MDMA.* British Journal of Clinical Pharmacology, 2002. **49**(2): p. 104-109.
215. Abbas, R., et al., *A Thorough QT Study to Evaluate the Effects of a Supratherapeutic Dose of Sertraline on Cardiac Repolarization in Healthy Subjects.* Clin Pharmacol Drug Dev, 2020. **9**(3): p. 307-320.
216. Otsuka, Y., *Paroxetine-induced QTc prolongation.* J Gen Fam Med, 2017. **18**(6): p. 442-445.
217. Vandeputte, C. and J.R. Docherty, *Vascular actions of 3,4-methylenedioxymethamphetamine in alpha(2A/D)- adrenoceptor knockout mice.* Eur J Pharmacol, 2002. **457**(1): p. 45-9.
218. Bexis, S. and J.R. Docherty, *Effects of MDMA, MDA and MDEA on blood pressure, heart rate, locomotor activity and body temperature in the rat involve alpha-adrenoceptors.* Br J Pharmacol, 2006. **147**(8): p. 926-34.
219. Bexis, S. and J.R. Docherty, *Role of alpha2A-adrenoceptors in the effects of MDMA on body temperature in the mouse.* Br J Pharmacol, 2005. **146**(1): p. 1-6.
220. Quinn, S.T., et al., *Blockade of noradrenaline transport abolishes 4-methylthioamphetamine-induced contraction of the rat aorta in vitro.* Auton Autacoid Pharmacol, 2006. **26**(4): p. 335-44.
221. Hysek, C.M., et al., *Effects of the alpha(2)-adrenergic agonist clonidine on the pharmacodynamics and pharmacokinetics of 3,4-methylenedioxymethamphetamine in healthy volunteers.* J Pharmacol Exp Ther, 2012. **340**(2): p. 286-94.
222. Hysek, C.M. and M.E. Liechti, *Effects of MDMA alone and after pretreatment with reboxetine, duloxetine, clonidine, carvedilol, and doxazosin on pupillary light reflex.* Psychopharmacology (Berl), 2012. **224**(3): p. 363-76.
223. Hysek, C.M., et al., *Carvedilol inhibits the cardiostimulant and thermogenic effects of MDMA in humans: Lost in translation.* Br J Pharmacol, 2013. **170**(6): p. 1273-5.
224. Hysek, C.M., et al., *Duloxetine inhibits effects of MDMA ("ecstasy") in vitro and in humans in a randomized placebo-controlled laboratory study.* PLoS One, 2012. **7**(5): p. e36476.

225. Fonseca, D.A., et al., *Hyperthermia Severely Affects the Vascular Effects of MDMA and Metabolites in the Human Internal Mammary Artery In Vitro.* Cardiovasc Toxicol, 2017. **17**(4): p. 405-416.
226. van der Schier, R., et al., *Opioid-induced respiratory depression: reversal by non-opioid drugs.* F1000Prime Rep, 2014. **6**: p. 79.
227. Goad, P.T., *Acute and subacute oral toxicity study of MDMA in rats (protocol number: EMD-AT-001, 1985)* 1986: Unpublished; MAPS [Earth Metabolic Design Laboratories].
228. Farah, R. and R. Farah, *Ecstasy (3,4-methylenedioxymethamphetamine)-induced inappropriate antidiuretic hormone secretion.* Pediatr Emerg Care, 2008. **24**(9): p. 615-7.
229. Esposito, P., et al., *The syndrome of inappropriate antidiuresis: pathophysiology, clinical management and new therapeutic options.* Nephron Clin Pract, 2011. **119**(1): p. c62-73; discussion c73.
230. Laycock, J., *Introduction to vasopressin.* Perspectives on vasopressin. London: World Scientific Publishing Company, Imperial College Press, 2010: p. 1-16.
231. Forsling, M., et al., *Arginine vasopressin release in response to the administration of 3,4- methylenedioxymethamphetamine ("ecstasy"): is metabolism a contributory factor?* J Pharm Pharmacol, 2001. **53**(10): p. 1357-63.
232. Tasker, J.G., et al., *Cell biology of oxytocin and vasopressin cells*, in *Hormones, brain and behavior*, Pfaff D.W., et al., Editors. 2002, Academic Press: London. p. 811-842.
233. Burbach, J., L. Young, and J. Russell, *Oxytocin: synthesis, secretion, and reproductive functions.* Knobil and Neill's physiology of reproduction, 2006. **2**: p. 3055-3128.
234. Hargreaves, G.A., et al., *High ambient temperature increases 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy")-induced Fos expression in a region-specific manner.* Neuroscience, 2007. **145**(2): p. 764-74.
235. Stanley, N., A. Salem, and R.J. Irvine, *The effects of co-administration of 3,4-methylenedioxymethamphetamine ("ecstasy") or para-methoxyamphetamine and moclobemide at elevated ambient temperatures on striatal 5-HT, body temperature and behavior in rats.* Neuroscience, 2007. **146**(1): p. 321-9.
236. McNamara, R., et al., *Caffeine promotes hyperthermia and serotonergic loss following co-administration of the substituted amphetamines, MDMA ("Ecstasy") and MDA ("Love").* Neuropharmacology, 2006. **50**(1): p. 69-80.
237. Kasai, M., et al., *The effects of mirtazapine and fluoxetine on hyperthermia induced by 3,4-methylenedioxymethamphetamine (MDMA) in rats.* Neurosci Lett, 2011. **499**(1): p. 24-7.
238. Thompson, M.R., et al., *Chronic fluoxetine treatment partly attenuates the long-term anxiety and depressive symptoms induced by MDMA ('Ecstasy') in rats.* Neuropsychopharmacology, 2004. **29**(4): p. 694-704.
239. Upreti, V.V. and N.D. Eddington, *Fluoxetine pretreatment effects pharmacokinetics of 3,4-methylenedioxymethamphetamine (MDMA, ECSTASY) in rat.* J Pharm Sci, 2008. **97**(4): p. 1593-605.
240. Mueller, M., et al., *Nonlinear pharmacokinetics of (+/-)3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") and its major metabolites in squirrel monkeys at plasma concentrations of MDMA that develop after typical psychoactive doses.* J Pharmacol Exp Ther, 2008. **327**(1): p. 38-44.

241. Mueller, M., et al., *Metabolism and disposition of 3,4-methylenedioxymethamphetamine ("ecstasy") in baboons after oral administration: comparison with humans reveals marked differences.* J Pharmacol Exp Ther, 2011. **338**(1): p. 310-7.
242. De Letter, E.A., et al., *Is vitreous humour useful for the interpretation of 3,4-methylenedioxymethamphetamine (MDMA) blood levels? Experimental approach with rabbits.* Int J Legal Med, 2000. **114**(1-2): p. 29-35.
243. Wan Aasim, W.R., S.C. Tan, and S.H. Gan, *Interspecies In Vitro Evaluation of Stereoselective Protein Binding for 3,4-Methylenedioxymethamphetamine.* Journal of Chemistry, 2017. **2017**: p. 8103726.
244. Scheidweiler, K.B., et al., *(+/-)-3,4-methylenedioxymethamphetamine and metabolite disposition in plasma and striatum of wild-type and multidrug resistance protein 1a knock-out mice.* J Anal Toxicol, 2011. **35**(7): p. 470-80.
245. Campbell, N.G., et al., *MDMA administration to pregnant Sprague-Dawley rats results in its passage to the fetal compartment.* Neurotoxicol Teratol, 2006. **28**(4): p. 459-65.
246. Williams, M.T., et al., *Absorption and clearance of +/-3,4-methylenedioxymethamphetamine from the plasma of neonatal rats.* Neurotoxicol Teratol, 2004. **26**(6): p. 849-56.
247. de la Torre, R. and M. Farre, *Neurotoxicity of MDMA (ecstasy): the limitations of scaling from animals to humans.* Trends Pharmacol Sci, 2004. **25**(10): p. 505-8.
248. Kolbrich, E.A., et al., *Plasma pharmacokinetics of 3,4-methylenedioxymethamphetamine after controlled oral administration to young adults.* Ther Drug Monit, 2008. **30**(3): p. 320-32.
249. Fantegrossi, W.E., et al., *Discriminative stimulus effects of 3,4-methylenedioxymethamphetamine and its enantiomers in mice: pharmacokinetic considerations.* J Pharmacol Exp Ther, 2009. **329**(3): p. 1006-15.
250. Mueller, M., et al., *Direct comparison of (+/-) 3,4-methylenedioxymethamphetamine ("ecstasy") disposition and metabolism in squirrel monkeys and humans.* Ther Drug Monit, 2009. **31**(3): p. 367-73.
251. Valtier, S., C.F. Phelix, and J.T. Cody, *Analysis of MDMA and its metabolites in urine and plasma following a neurotoxic dose of MDMA.* J Anal Toxicol, 2007. **31**(3): p. 138-43.
252. Jamali, B., et al., *Evaluation of the Ecstasy influence on tramadol and its main metabolite plasma concentration in rats.* Drug Metab Pers Ther, 2017. **32**(3): p. 137-145.
253. Kuwayama, K., et al., *Interaction of 3,4-methylenedioxymethamphetamine and methamphetamine during metabolism by in vitro human metabolic enzymes and in rats.* J Forensic Sci, 2012. **57**(4): p. 1008-13.
254. Moon, K.H., et al., *Mechanism of 3,4-methylenedioxymethamphetamine (MDMA, ecstasy)-mediated mitochondrial dysfunction in rat liver.* Proteomics, 2008. **8**(18): p. 3906-18.
255. Bonkale, W.L. and M.C. Austin, *3,4-Methylenedioxymethamphetamine induces differential regulation of tryptophan hydroxylase 2 protein and mRNA levels in the rat dorsal raphe nucleus.* Neuroscience, 2008. **155**(1): p. 270-6.
256. Schenk, S., et al., *Effects of repeated exposure to MDMA on 5HT1a autoreceptor function: behavioral and neurochemical responses to 8-OHDPAT.* Psychopharmacology (Berl), 2013. **227**(2): p. 355-61.

257. Adori, C., et al., *Recovery and aging of serotonergic fibers after single and intermittent MDMA treatment in Dark Agouti rat.* J Comp Neurol, 2011. **519**(12): p. 2353-78.
258. Mueller, M., et al., *Single oral doses of (+/-) 3,4-methylenedioxymethamphetamine ('Ecstasy') produce lasting serotonergic deficits in non-human primates: relationship to plasma drug and metabolite concentrations.* Int J Neuropsychopharmacol, 2013. **16**(4): p. 791-801.
259. de la Torre, R., et al., *MDMA, methamphetamine, and CYP2D6 pharmacogenetics: what is clinically relevant?* Front Genet, 2012. **3**: p. 235.
260. Peiro, A.M., et al., *Human pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) after repeated doses taken 2 h apart.* Psychopharmacology (Berl), 2013. **225**(4): p. 883-93.
261. St Omer, V.E., et al., *Behavioral and neurochemical effects of prenatal methylenedioxymethamphetamine (MDMA) exposure in rats.* Neurotoxicol Teratol, 1991. **13**(1): p. 13-20.
262. Plessinger, M.A., *Prenatal exposure to amphetamines. Risks and adverse outcomes in pregnancy.* Obstet Gynecol Clin North Am, 1998. **25**(1): p. 119-38.
263. Kwack, S.J., et al., *A One-Generation Reproductive Toxicity Study of 3,4-Methylenedioxy-N-Methamphetamine (MDMA, Ecstasy), an Amphetamine Derivative, in C57BL/6 Mice.* J Toxicol Environ Health A, 2014. **77**(22-24): p. 1431-42.
264. Connor, T.J., et al., *Methylenedioxymethamphetamine (MDMA; Ecstasy) suppresses IL-1beta and TNF-alpha secretion following an in vivo lipopolysaccharide challenge.* Life Sci, 2000. **67**(13): p. 1601-12.
265. Pennock, J.W., et al., *3,4-Methylenedioxymethamphetamine increases susceptibility to genital herpes simplex virus infection in mice.* J Infect Dis, 2009. **200**(8): p. 1247-50.
266. Liu, X., et al., *3,4-Methylenedioxymethamphetamine causes cytotoxicity on 661W cells through inducing macrophage polarization.* Cutan Ocul Toxicol, 2018. **37**(2): p. 143-150.
267. de Paula, V.F., et al., *Methylenedioxymethamphetamine (Ecstasy) decreases neutrophil activity and alters leukocyte distribution in bone marrow, spleen and blood.* Neuroimmunomodulation, 2009. **16**(3): p. 191-200.
268. Boyle, N.T. and T.J. Connor, *MDMA ("Ecstasy") suppresses the innate IFN-gamma response in vivo: a critical role for the anti-inflammatory cytokine IL-10.* Eur J Pharmacol, 2007. **572**(2-3): p. 228-38.
269. Stankevicius, D., et al., *3,4-methylenedioxymethamphetamine (ecstasy) decreases inflammation and airway reactivity in a murine model of asthma.* Neuroimmunomodulation, 2012. **19**(4): p. 209-19.
270. Fernandez-Castillo, N., et al., *Active and passive MDMA ('ecstasy') intake induces differential transcriptional changes in the mouse brain.* Genes Brain Behav, 2012. **11**(1): p. 38-51.
271. Passos, I.C., et al., *Inflammatory markers in post-traumatic stress disorder: a systematic review, meta-analysis, and meta-regression.* Lancet Psychiatry, 2015. **2**(11): p. 1002-12.
272. Miller, C.A. and J.D. Sweatt, *Covalent modification of DNA regulates memory formation.* Neuron, 2007. **53**(6): p. 857-69.

273. Unternaehrer, E., et al., *Childhood maternal care is associated with DNA methylation of the genes for brain-derived neurotrophic factor (BDNF) and oxytocin receptor (OXTR) in peripheral blood cells in adult men and women.* Stress, 2015. **18**(4): p. 451-61.
274. Curry, D.W., et al., *Sensitization to the prosocial effects of 3,4-methylenedioxymethamphetamine (MDMA).* Neuropharmacology, 2019.
275. Nardou, R., et al., *Oxytocin-dependent reopening of a social reward learning critical period with MDMA.* Nature, 2019. **569**(7754): p. 116-120.
276. Ly, C., et al., *Psychedelics Promote Structural and Functional Neural Plasticity.* Cell Rep, 2018. **23**(11): p. 3170-3182.
277. Young, M.B., et al., *3,4-Methylenedioxymethamphetamine facilitates fear extinction learning.* Transl Psychiatry, 2015. **5**: p. e634.
278. Budzynska, B., et al., *Acute MDMA and Nicotine Co-administration: Behavioral Effects and Oxidative Stress Processes in Mice.* Front Behav Neurosci, 2018. **12**: p. 149.
279. Hake, H.S., et al., *3,4-methylenedioxymethamphetamine (MDMA) impairs the extinction and reconsolidation of fear memory in rats.* Physiol Behav, 2019. **199**: p. 343-350.
280. Peng, W., et al., *Synaptotagmin I and IV are differentially regulated in the brain by the recreational drug 3,4-methylenedioxymethamphetamine (MDMA).* Brain Res Mol Brain Res, 2002. **108**(1-2): p. 94-101.
281. Petschner, P., et al., *Downregulation of the Vitamin D Receptor Regulated Gene Set in the Hippocampus After MDMA Treatment.* Front Pharmacol, 2018. **9**: p. 1373.
282. Petschner, P., et al., *Gene expression analysis indicates reduced memory and cognitive functions in the hippocampus and increase in synaptic reorganization in the frontal cortex 3 weeks after MDMA administration in Dark Agouti rats.* BMC Genomics, 2018. **19**(1): p. 580.
283. Pompei, P., et al., *Preprotachykinin A gene expression after administration of 3,4-methylene dioxymethamphetamine (Ecstasy).* Eur J Pharmacol, 2002. **450**(3): p. 245.
284. Sprague, J.E., et al. *Effects of antisense oligonucleotide alteration of MAO-B gene expression on MDMA-induced serotonergic neurotoxicity*. in *Society for Neuroscience*. 1999. Miami, FL.
285. Thiriet, N., et al., *Analysis of ecstasy (MDMA)-induced transcriptional responses in the rat cortex.* Faseb J, 2002. **16**(14): p. 1887-94.
286. Martinez-Turrillas, R., et al., *Differential effects of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") on BDNF mRNA expression in rat frontal cortex and hippocampus.* Neurosci Lett, 2006. **402**(1-2): p. 126-30.
287. Sandrini, M., et al., *Causal role of prefrontal cortex in strengthening of episodic memories through reconsolidation.* Curr Biol, 2013. **23**(21): p. 2181-4.
288. Llado-Pelfort, L., et al., *5-HT1A receptor agonists enhance pyramidal cell firing in prefrontal cortex through a preferential action on GABA interneurons.* Cereb Cortex, 2012. **22**(7): p. 1487-97.
289. Karpova, N.N., *Role of BDNF epigenetics in activity-dependent neuronal plasticity.* Neuropharmacology, 2014. **76 Pt C**: p. 709-18.

290. Biezonski, D.K. and J.S. Meyer, *Effects of 3,4-methylenedioxymethamphetamine (MDMA) on serotonin transporter and vesicular monoamine transporter 2 protein and gene expression in rats: implications for MDMA neurotoxicity.* J Neurochem, 2010. **112**(4): p. 951-62.
291. Kindlundh-Hogberg, A.M., P. Svenningsson, and H.B. Schioth, *Quantitative mapping shows that serotonin rather than dopamine receptor mRNA expressions are affected after repeated intermittent administration of MDMA in rat brain.* Neuropharmacology, 2006. **51**(4): p. 838-47.
292. Salzmann, J., et al., *Analysis of transcriptional responses in the mouse dorsal striatum following acute 3,4-methylenedioxymethamphetamine (ecstasy): identification of extracellular signal-regulated kinase-controlled genes.* Neuroscience, 2006. **137**(2): p. 473-82.
293. Yubero-Lahoz, S., et al., *Changes in serotonin transporter (5-HTT) gene expression in peripheral blood cells after MDMA intake.* Psychopharmacology (Berl), 2015. **232**(11): p. 1921-9.
294. Fantegrossi, W.E., et al., *Behavioral and neurochemical consequences of long-term intravenous self-administration of MDMA and its enantiomers by rhesus monkeys.* Neuropsychopharmacology, 2004. **29**(7): p. 1270-81.
295. Highgate, Q. and S. Schenk, *Comparison of the effects of abstinence on MDMA and cocaine self-administration in rats.* Psychopharmacology (Berl), 2018. **235**(11): p. 3233-3241.
296. Schenk, S., et al., *Development, maintenance and temporal pattern of self-administration maintained by ecstasy (MDMA) in rats.* Psychopharmacology (Berl), 2003. **169**(1): p. 21-7.
297. Trigo, J.M., et al., *A reliable model of intravenous MDMA self-administration in naive mice.* Psychopharmacology (Berl), 2006. **184**(2): p. 212-20.
298. Oberlender, R. and D.E. Nichols, *Drug discrimination studies with MDMA and amphetamine.* Psychopharmacology (Berl), 1988. **95**(1): p. 71-6.
299. Lile, J.A., J.T. Ross, and M.A. Nader, *A comparison of the reinforcing efficacy of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") with cocaine in rhesus monkeys.* Drug Alcohol Depend, 2005. **78**(2): p. 135-40.
300. Wang, Z. and W.L. Woolverton, *Estimating the relative reinforcing strength of (+/-)-3,4-methylenedioxymethamphetamine (MDMA) and its isomers in rhesus monkeys: comparison to (+)-methamphetamine.* Psychopharmacology (Berl), 2007. **189**(4): p. 483-8.
301. Robledo, P., et al., *Study of the behavioural responses related to the potential addictive properties of MDMA in mice.* Naunyn Schmiedebergs Arch Pharmacol, 2004. **369**(3): p. 338-49.
302. Glennon, R.A., *Arylalkylamine drugs of abuse: an overview of drug discrimination studies.* Pharmacol Biochem Behav, 1999. **64**(2): p. 251-6.
303. Goodwin, A.K., D.M. Pynnonen, and L.E. Baker, *Serotonergic-dopaminergic mediation of MDMA's discriminative stimulus effects in a three-choice discrimination.* Pharmacol Biochem Behav, 2003. **74**(4): p. 987-95.
304. Schenk, S. and Q. Highgate, *Dopamine and serotonin antagonists fail to alter the discriminative stimulus properties of +/-methylenedioxymethamphetamine.* Behav Pharmacol, 2018.
305. Smith, D.A., B.E. Blough, and M.L. Banks, *Cocaine-like discriminative stimulus effects of amphetamine, cathinone, methamphetamine, and their 3,4-*

methylenedioxy analogs in male rhesus monkeys. Psychopharmacology (Berl), 2017. **234**(1): p. 117-127.
306. Gaston, T.R., Rasmussen, G. T., *Identification of 3,4-methylenedioxy-n-methylamphetamine;*. Microgram, 1972. **5**: p. 60-63.
307. Stolaroff, M., *The Secret Chief Revealed: Conversations with a pioneer of the underground therapy movement.* 2004, Sarasota FL: Multidisciplinary Association for Psychedelic Studies.
308. Carlson, R.G., et al., *Drug use practices among MDMA/ecstasy users in Ohio: a latent class analysis.* Drug Alcohol Depend, 2005. **79**(2): p. 167-79.
309. Sumnall, H.R., J.C. Cole, and L. Jerome, *The varieties of ecstatic experience: an exploration of the subjective experiences of ecstasy.* J Psychopharmacol, 2006. **20**(5): p. 670-82.
310. Cole, J.C. and H.R. Sumnall, *Altered states: the clinical effects of Ecstasy.* Pharmacol Ther, 2003. **98**(1): p. 35-58.
311. Baggott, M., et al., *Chemical analysis of ecstasy pills.* Jama, 2000. **284**(17): p. 2190.
312. Cole, J.C., et al., *The content of ecstasy tablets: implications for the study of their long-term effects.* Addiction, 2002. **97**(12): p. 1531-6.
313. Tanner-Smith, E.E., *Pharmacological content of tablets sold as "ecstasy": results from an online testing service.* Drug Alcohol Depend, 2006. **83**(3): p. 247-54.
314. Brunt, T.M., et al., *Drug testing in Europe: monitoring results of the Trans European Drug Information (TEDI) project.* Drug Test Anal, 2017. **9**(2): p. 188-198.
315. Halpern, J.H., et al., *Residual neurocognitive features of long-term ecstasy users with minimal exposure to other drugs.* Addiction, 2011. **106**(4): p. 777-86.
316. Baggott, M.J., *Preventing problems in Ecstasy users: reduce use to reduce harm.* J Psychoactive Drugs, 2002. **34**(2): p. 145-62.
317. Gore, S.M., *Fatal uncertainty: death-rate from use of ecstasy or heroin.* Lancet, 1999. **354**(9186): p. 1265-6.
318. United Nations Office on Drugs and Crime, *World Drug Report*. 2020, United Nations Office on Drugs and Crime: New York, NY.
319. Green, A.R., E. O'Shea, and M.I. Colado, *A review of the mechanisms involved in the acute MDMA (ecstasy)-induced hyperthermic response.* Eur J Pharmacol, 2004. **500**(1-3): p. 3-13.
320. Liechti, M.E., I. Kunz, and H. Kupferschmidt, *Acute medical problems due to Ecstasy use. Case-series of emergency department visits.* Swiss Med Wkly, 2005. **135**(43-44): p. 652-7.
321. Rosenson, J., et al., *Patterns of ecstasy-associated hyponatremia in California.* Ann Emerg Med, 2007. **49**(2): p. 164-71, 171 e1.
322. Henry, J.A. and J.G. Rella, *Medical risks associated with MDMA use*, in *Ecstasy: A Complete Guide*, J. Holland, Editor. 2001, Inner Traditions: Rochester, VT. p. 71-86.
323. Hall, A.P. and J.A. Henry, *Acute toxic effects of 'Ecstasy' (MDMA) and related compounds: overview of pathophysiology and clinical management.* Br J Anaesth, 2006. **96**(6): p. 678-85.
324. Cregg, M.T. and J.A. Tracey, *Ecstasy abuse in Ireland.* Ir Med J, 1993. **86**(4): p. 118-20.

325. Williams, H., et al., *"Saturday night fever": ecstasy related problems in a London accident and emergency department.* J Accid Emerg Med, 1998. **15**(5): p. 322-6.
326. Armenian, P., et al., *Multiple MDMA (Ecstasy) overdoses at a rave event: a case series.* J Intensive Care Med, 2013. **28**(4): p. 252-8.
327. CDC, *Ecstasy overdoses at a New Year's Eve rave--Los Angeles, California, 2010.* MMWR Morb Mortal Wkly Rep, 2010. **59**(22): p. 677-81.
328. Angelique, F., et al., *Postmortem Hyperthermia: Two Case Reports and a Review of the Literature.* Am J Forensic Med Pathol, 2018. **39**(4): p. 364-366.
329. Gowing, L.R., et al., *The health effects of ecstasy: a literature review.* Drug Alcohol Rev, 2002. **21**(1): p. 53-63.
330. Grunau, B.E., M.O. Wiens, and M. Greidanus, *Dantrolene for the treatment of MDMA toxicity.* CJEM, 2010. **12**(5): p. 457-9.
331. Russell, T., et al., *Ecstacy-induced delayed rhabdomyolysis and neuroleptic malignant syndrome in a patient with a novel variant in the ryanodine receptor type 1 gene.* Anaesthesia, 2012. **67**(9): p. 1021-4.
332. Shah, H.V., G.H. Irvine, and M. Bradley, *Rhabdomyolysis of the masseter muscle: case report.* Br J Oral Maxillofac Surg, 2008. **46**(2): p. 138-40.
333. Davies, O., et al., *Full recovery after severe serotonin syndrome, severe rhabdomyolysis, multi-organ failure and disseminated intravascular coagulopathy from MDMA.* Heart Lung, 2014. **43**(2): p. 117-9.
334. Hall, A.P., et al., *An unusual case of Ecstasy poisoning.* Intensive Care Med, 1996. **22**(7): p. 670-1.
335. Logan, A.S., et al., *Survival following 'Ecstasy' ingestion with a peak temperature of 42 degrees C.* Anaesthesia, 1993. **48**(11): p. 1017-8.
336. Singarajah, C. and N.G. Lavies, *An overdose of ecstasy. A role for dantrolene.* Anaesthesia, 1992. **47**(8): p. 686-7.
337. Bedford Russell, A.R., R.H. Schwartz, and S. Dawling, *Accidental ingestion of 'Ecstasy' (3,4-methylenedioxymethylamphetamine).* Arch Dis Child, 1992. **67**(9): p. 1114-5.
338. Nimmo, S.M., et al., *Drug-induced hyperthermia.* Anaesthesia, 1993. **48**(10): p. 892-5.
339. Murthy, B.V., R.G. Wilkes, and N.B. Roberts, *Creatine kinase isoform changes following Ecstasy overdose.* Anaesth Intensive Care, 1997. **25**(2): p. 156-9.
340. Ramcharan, S., et al., *Survival after massive ecstasy overdose.* J Toxicol Clin Toxicol, 1998. **36**(7): p. 727-31.
341. Screaton, G.R., et al., *Hyperpyrexia and rhabdomyolysis after MDMA ("ecstasy") abuse.* Lancet, 1992. **339**(8794): p. 677-8.
342. Montgomery, H. and S. Myerson, *3,4-methylenedioxymethamphetamine (MDMA, or "ecstasy") and associated hypoglycemia.* Am J Emerg Med, 1997. **15**(2): p. 218.
343. Williams, A. and R. Unwin, *Prolonged elevation of serum creatine kinase (CK) without renal failure after ingestion of ecstasy.* Nephrol Dial Transplant, 1997. **12**(2): p. 361-2.
344. Hayner, G.N. and H. McKinney, *MDMA. The dark side of ecstasy.* J Psychoactive Drugs, 1986. **18**(4): p. 341-7.
345. Jahns, F.P., A. Pineau Mitchell, and G. Auzinger, *Too Hot to Handle: A Case Report of Extreme Pyrexia After MDMA Ingestion.* Ther Hypothermia Temp Manag, 2018.

346. Toth, A.R. and T. Varga, *Myocardium and striated muscle damage caused by licit or illicit drugs.* Leg Med (Tokyo), 2009. **11 Suppl 1**: p. S484-7.
347. Vanden Eede, H., et al., *Rhabdomyolysis in MDMA intoxication: a rapid and underestimated killer. "Clean" Ecstasy, a safe party drug?* J Emerg Med, 2012. **42**(6): p. 655-8.
348. Lang, J., et al., *Fatal Ecstasy-induced malignant hyperthermia with rhabdomyolysis. A case report.* Romanian Journal of Legal Medicine, 2016. **24**(3): p. 212-215.
349. Milroy, C.M., J.C. Clark, and A.R. Forrest, *Pathology of deaths associated with "ecstasy" and "eve" misuse.* J Clin Pathol, 1996. **49**(2): p. 149-53.
350. Sadeghian, S., et al., *Two ecstasy-induced myocardial infarctions during a three month period in a young man.* Arch Iran Med, 2007. **10**(3): p. 409-12.
351. Diffley, M., et al., *Catecholaminergic polymorphic ventricular tachycardia found in an adolescent after a methylenedioxymethamphetamine and marijuana-induced cardiac arrest.* Crit Care Med, 2012. **40**(7): p. 2223-6.
352. Hoggett, K., D. McCoubrie, and D.M. Fatovich, *Ecstasy-induced acute coronary syndrome: something to rave about.* Emerg Med Australas, 2012. **24**(3): p. 339-42.
353. Moller, M., et al., *Ecstasy-induced myocardial infarction in a teenager: rare complication of a widely used illicit drug.* Clin Res Cardiol, 2010. **99**(12): p. 849-51.
354. Kapoor, A. and K.S. Jackson, *Seizures presenting in pregnancy: eclampsia or something else?* J Obstet Gynaecol, 2013. **33**(6): p. 630-1.
355. Okunoye, G.O. and P. Dutton, *Acute myocardial infarction in pregnancy following unlicensed use of methylenedioxymethamphetamine ('Ecstasy').* Scott Med J, 2013. **58**(3): p. e4-6.
356. Montastruc, F., et al., *Valvular heart disease in a patient taking 3,4-methylenedioxymethamphetamine (MDMA, 'Ecstasy').* Br J Clin Pharmacol, 2012. **74**(3): p. 547-8.
357. Mizia-Stec, K., et al., *Severe dilated cardiomyopathy as a consequence of Ecstasy intake.* Cardiovasc Pathol, 2008. **17**(4): p. 250-3.
358. Hua, Y.S., et al., *Contraction band necrosis in two ecstasy abusers: a latent lethal lesion associated with ecstasy.* Am J Forensic Med Pathol, 2009. **30**(3): p. 295-7.
359. Sano, R., et al., *A fatal case of myocardial damage due to misuse of the "designer drug" MDMA.* Leg Med (Tokyo), 2009. **11**(6): p. 294-7.
360. Dowling, G.P., E.T.d. McDonough, and R.O. Bost, *'Eve' and 'Ecstasy'. A report of five deaths associated with the use of MDEA and MDMA.* Jama, 1987. **257**(12): p. 1615-7.
361. Suarez, R.V. and R. Riemersma, *"Ecstasy" and sudden cardiac death.* Am J Forensic Med Pathol, 1988. **9**(4): p. 339-41.
362. Lora-Tamayo, C., T. Tena, and A. Rodriguez, *Amphetamine derivative related deaths.* Forensic Sci Int, 1997. **85**(2): p. 149-57.
363. Bingham, C., et al., *Necrotizing renal vasculopathy resulting in chronic renal failure after ingestion of methamphetamine and 3,4-methylenedioxymethamphetamine ('ecstasy').* Nephrol Dial Transplant, 1998. **13**(10): p. 2654-5.

364. Ghatol, A. and A. Kazory, *Ecstasy-associated acute severe hyponatremia and cerebral edema: a role for osmotic diuresis?* J Emerg Med, 2012. **42**(6): p. e137-40.
365. Beuerle, J.R. and F. Barrueto, Jr., *Neurogenic bladder and chronic urinary retention associated with MDMA abuse.* J Med Toxicol, 2008. **4**(2): p. 106-8.
366. Bryden, A.A., P.J. Rothwell, and P.H. O'Reilly, *Urinary retention with misuse of "ecstasy".* BMJ, 1995. **310**(6978): p. 504.
367. Delgado, J.H., et al., *Acute, transient urinary retention from combined ecstasy and methamphetamine use.* J Emerg Med, 2004. **26**(2): p. 173-5.
368. Holden, R. and M.A. Jackson, *Near-fatal hyponatraemic coma due to vasopressin over-secretion after "ecstasy" (3,4-MDMA).* Lancet, 1996. **347**(9007): p. 1052.
369. Henry, J.A., et al., *Low-dose MDMA ("ecstasy") induces vasopressin secretion.* Lancet, 1998. **351**(9118): p. 1784.
370. Gomez-Balaguer, M., et al., *Syndrome of inappropriate antidiuretic hormone secretion and "designer drugs" (ecstasy).* J Pediatr Endocrinol Metab, 2000. **13**(4): p. 437-8.
371. Hegadoren, K.M., G.B. Baker, and M. Bourin, *3,4-Methylenedioxy analogues of amphetamine: defining the risks to humans.* Neurosci Biobehav Rev, 1999. **23**(4): p. 539-53.
372. Woodrow, G., P. Harnden, and J.H. Turney, *Acute renal failure due to accelerated hypertension following ingestion of 3,4-methylenedioxymethamphetamine ('ecstasy').* Nephrol Dial Transplant, 1995. **10**(3): p. 399-400.
373. Cadier, M.A. and J.A. Clarke, *Ecstasy and Whizz at a rave resulting in a major burn plus complications.* Burns, 1993. **19**(3): p. 239-40.
374. Fahal, I.H., et al., *Acute renal failure after ecstasy.* Bmj, 1992. **305**(6844): p. 29.
375. Maxwell, D.L., M.I. Polkey, and J.A. Henry, *Hyponatraemia and catatonic stupor after taking "ecstasy".* Bmj, 1993. **307**(6916): p. 1399.
376. Satchell, S.C. and M. Connaughton, *Inappropriate antidiuretic hormone secretion and extreme rises in serum creatinine kinase following MDMA ingestion.* Br J Hosp Med, 1994. **51**(9): p. 495.
377. Thakkar, A., et al., *A Case of MDMA-Associated Cerebral and Pulmonary Edema Requiring ECMO.* Case Rep Crit Care, 2017. **2017**: p. 6417012.
378. Claffey, C., *A 26-year-old woman with sudden onset cerebral edema.* J Emerg Nurs, 2011. **37**(1): p. 55-6.
379. Gritti, P., et al., *Are we aware of ecstasy effects?* Intern Emerg Med, 2009. **4**(2): p. 175-7.
380. Parr, M.J., H.M. Low, and P. Botterill, *Hyponatraemia and death after "ecstasy" ingestion.* Med J Aust, 1997. **166**(3): p. 136-7.
381. O'Connor, A., et al., *Death from hyponatraemia-induced cerebral oedema associated with MDMA ("Ecstasy") use.* N Z Med J, 1999. **112**(1091): p. 255-6.
382. Dar, K.J. and M.E. McBrien, *MDMA induced hyperthermia: report of a fatality and review of current therapy.* Intensive Care Med, 1996. **22**(9): p. 995-6.
383. Gilbert, J.D. and R.W. Byard, *Fatal Diabetic Ketoacidosis-A Potential Complication of MDMA (Ecstasy) Use.* J Forensic Sci, 2018. **63**(3): p. 939-941.
384. Mikula, T., J. Kozlowska, and A. Wiercinska-Drapalo, *Alcohol and ecstasy (MDMA-3,4-methylenedioxymethamphetamine) overdose as a reason for acute hepatitis with gall bladder inflammation.* Drug Alcohol Rev, 2009. **28**(6): p. 685.

385. Payance, A., et al., *Severe chronic hepatitis secondary to prolonged use of ecstasy and cocaine.* Clin Res Hepatol Gastroenterol, 2013. **37**(5): p. e109-13.
386. Nadkarni, G.N., et al., *Serotonin syndrome, disseminated intravascular coagulation, and hepatitis after a single ingestion of MDMA in an Asian woman.* Am J Ther, 2014. **21**(4): p. e117-9.
387. Colak, Y., et al., *Ecstasy induced fatal hepatic failure.* J Gastrointestin Liver Dis, 2011. **20**(2): p. 215-6.
388. Chadwick, I.S., et al., *Ecstasy, 3-4 methylenedioxymethamphetamine (MDMA), a fatality associated with coagulopathy and hyperthermia.* J R Soc Med, 1991. **84**(6): p. 371.
389. Campkin, N.J. and U.M. Davies, *Treatment of 'ecstasy' overdose with dantrolene.* Anaesthesia, 1993. **48**(1): p. 82-3.
390. Fineschi, V. and A. Masti, *Fatal poisoning by MDMA (ecstasy) and MDEA: a case report.* Int J Legal Med, 1996. **108**(5): p. 272-5.
391. Wollner, K., et al., *[Death after the intake of amphetamine/ecstasy: two case reports].* Arch Kriminol, 2015. **235**(1-2): p. 53-61.
392. Clark, A.D. and N. Butt, *Ecstasy-induced very severe aplastic anaemia complicated by invasive pulmonary mucormycosis treated with allogeneic peripheral blood progenitor cell transplant.* Clin Lab Haematol, 1997. **19**(4): p. 279-81.
393. Marsh, J.C., et al., *Aplastic anaemia following exposure to 3,4-methylenedioxymethamphetamine ('Ecstasy').* Br J Haematol, 1994. **88**(2): p. 281-5.
394. Richman, J. and A. Ferber, *Severe aplastic anemia with hot pockets following daily Ecstasy ingestion.* Am J Hematol, 2008. **83**(4): p. 321-2.
395. Gomez-Fernandez, C., et al., *Facial eruption related to snorting Ecstasy.* Eur J Dermatol, 2010. **20**(6): p. 853-4.
396. Schroder, A.S., H. Andresen-Streichert, and S. Anders, *Swollen Lips After a Night of Partying-An Allergic Reaction to Ecstasy?* J Forensic Sci, 2019.
397. Sauvageau, A., *Death from a possible anaphylactic reaction to ecstasy.* Clin Toxicol (Phila), 2008. **46**(2): p. 156.
398. Kahn, D.E., N. Ferraro, and R.J. Benveniste, *3 cases of primary intracranial hemorrhage associated with "Molly", a purified form of 3,4-methylenedioxymethamphetamine (MDMA).* J Neurol Sci, 2012. **323**(1-2): p. 257-60.
399. Kaku, D.A. and D.H. Lowenstein, *Emergence of recreational drug abuse as a major risk factor for stroke in young adults.* Ann Intern Med, 1990. **113**(11): p. 821-7.
400. Hughes, J.C., M. McCabe, and R.J. Evans, *Intracranial haemorrhage associated with ingestion of 'ecstasy'.* Arch Emerg Med, 1993. **10**(4): p. 372-4.
401. De Smet, K., et al., *Bilateral globus pallidus infarcts in ecstasy use.* JBR-BTR, 2011. **94**(2): p. 93.
402. Gardner, H., et al., *Acute hippocampal sclerosis following ecstasy ingestion.* Neurology, 2009. **73**(7): p. 567-9.
403. Nifosi, F., et al., *Hippocampal remodelling after MDMA neurotoxicity: a single case study.* World J Biol Psychiatry, 2009. **10**(4 Pt 3): p. 961-8.
404. Ruis, C., et al., *Cognitive disorders after sporadic ecstasy use? A case report.* Neurocase, 2014.

405. Bruggemann, N., et al., *Acute amnestic syndrome due to MDMA exposure.* J Neurol, 2016. **263**(5): p. 1022-1023.
406. Spatt, J., B. Glawar, and B. Mamoli, *A pure amnestic syndrome after MDMA ("ecstasy") ingestion.* J Neurol Neurosurg Psychiatry, 1997. **62**(4): p. 418-9.
407. Squier, M.V., et al., *Death after ecstasy ingestion: neuropathological findings.* J Neurol Neurosurg Psychiatry, 1995. **58**(6): p. 756.
408. Ginat, D.T., *MRI of toxic leukoencephalopathy syndrome associated with methylenedioxymethamphetamine.* Neurology, 2015. **84**(7): p. 757.
409. Hauw, F., et al., *Isolated persistent acute global amnesia after acute abuse of 3,4-methylenedioxy-methamphetamine (MDMA).* J Neurol Sci, 2018. **386**: p. 36-38.
410. Brand, H.S., S.N. Dun, and A.V. Nieuw Amerongen, *Ecstasy (MDMA) and oral health.* Br Dent J, 2008. **204**(2): p. 77-81.
411. Duxbury, A.J., *Ecstasy--dental implications.* Br Dent J, 1993. **175**(1): p. 38.
412. Nixon, P.J., C.C. Youngson, and A. Beese, *Tooth surface loss: does recreational drug use contribute?* Clin Oral Investig, 2002. **6**(2): p. 128-30.
413. Marchesi, C., M. Tonna, and C. Maggini, *Obsessive-compulsive disorder followed by psychotic episode in long-term ecstasy misuse.* World J Biol Psychiatry, 2009. **10**(4 Pt 2): p. 599-602.
414. Potash, M.N., K.A. Gordon, and K.L. Conrad, *Persistent Psychosis and Medical Complications After a Single Ingestion of MDMA "Ecstasy": A Case Report and Review of the Literature.* Psychiatry (Edgmont), 2009. **6**(7): p. 40-4.
415. Tabatabaei, S.A., M. Soleimani, and A. Khodabandeh, *A case of autoenucleation associated with a contralateral field defect.* Orbit, 2011. **30**(3): p. 165-8.
416. Mutlu, H., et al., *'Ecstasy'(MDMA)-induced pneumomediastinum and epidural pneumatosis.* Diagn Interv Radiol, 2005. **11**(3): p. 150-1.
417. Onwudike, M., *Ecstasy induced retropharyngeal emphysema.* J Accid Emerg Med, 1996. **13**(5): p. 359-61.
418. Pittman, J.A. and J.C. Pounsford, *Spontaneous pneumomediastinum and Ecstasy abuse.* J Accid Emerg Med, 1997. **14**(5): p. 335-6.
419. Quin, G.I., G.M. McCarthy, and D.K. Harries, *Spontaneous pneumomediastinum and ecstasy abuse.* J Accid Emerg Med, 1999. **16**(5): p. 382.
420. Gungadeen, A. and J. Moor, *Extensive subcutaneous emphysema and pneumomediastinum after ecstasy ingestion.* Case Rep Otolaryngol, 2013. **2013**: p. 795867.
421. Clause, A.L., et al., *Spontaneous pneumomediastinum and epidural pneumatosis after oral ecstasy consumption.* Acta Clin Belg, 2014. **69**(2): p. 146-8.
422. Peters, N.F., R. Gosselin, and K.L. Verstraete, *A rare case of diffuse alveolar hemorrhage following oral amphetamine intake.* JBR-BTR, 2014. **97**(1): p. 42-3.
423. Barrett, P.J., *'Ecstasy' misuse--overdose or normal dose?* Anaesthesia, 1993. **48**(1): p. 83.
424. Van den Kerckhove, E., et al., *Airway Necrosis and Barotrauma after Ecstasy Inhalation.* Am J Respir Crit Care Med, 2017. **196**(1): p. 105-106.
425. O'Neill, D. and J.K. Dart, *Methylenedioxyamphetamine ('Ecstasy') associated keratopathy.* Eye, 1993. **7**(Pt 6): p. 805-6.
426. Schroeder, B. and S. Brieden, *Bilateral sixth nerve palsy associated with MDMA ("ecstasy") abuse.* Am J Ophthalmol, 2000. **129**(3): p. 408-9.
427. Schifano, F., et al., *Death rates from ecstasy (MDMA, MDA) and polydrug use in England and Wales 1996-2002.* Hum Psychopharmacol, 2003. **18**(7): p. 519-24.

428. Nadesan, K., C. Kumari, and M. Afiq, *Dancing to death: A case of heat stroke.* J Forensic Leg Med, 2017. **50**: p. 1-5.
429. Escalante, F.A., F. Del Bano, and A. Supervia, *MDMA-induced angioedema treated with icatibant.* Clin Toxicol (Phila), 2015. **53**(10): p. 1148-9.
430. Zaami, S., et al., *Myocardial bridging and ecstasy: A fatal combination involving a 22year-old male.* Int J Cardiol, 2016. **220**: p. 835-6.
431. Nedahl, M., S.S. Johansen, and K. Linnet, *Postmortem Brain-Blood Ratios of Amphetamine, Cocaine, Ephedrine, MDMA and Methylphenidate.* J Anal Toxicol, 2019. **43**(5): p. 378-384.
432. Parrott, A.C., *MDMA and temperature: a review of the thermal effects of 'Ecstasy' in humans.* Drug Alcohol Depend, 2012. **121**(1-2): p. 1-9.
433. Greene, S.L., et al., *Multiple toxicity from 3,4-methylenedioxymethamphetamine ("ecstasy").* Am J Emerg Med, 2003. **21**(2): p. 121-4.
434. Dafters, R.I., *Hyperthermia following MDMA administration in rats: effects of ambient temperature, water consumption, and chronic dosing.* Physiol Behav, 1995. **58**(5): p. 877-82.
435. Docherty, J.R. and A.R. Green, *The role of monoamines in the changes in body temperature induced by 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) and its derivatives.* Br J Pharmacol, 2010. **160**(5): p. 1029-44.
436. Martin, T.L., D.A. Chiasson, and S.J. Kish, *Does hyperthyroidism increase risk of death due to the ingestion of ecstasy?* J Forensic Sci, 2007. **52**(4): p. 951-3.
437. Sprague, J.E., et al., *Roles of norepinephrine, free Fatty acids, thyroid status, and skeletal muscle uncoupling protein 3 expression in sympathomimetic-induced thermogenesis.* J Pharmacol Exp Ther, 2007. **320**(1): p. 274-80.
438. Perez, J.A., Jr., E.L. Arsura, and S. Strategos, *Methamphetamine-related stroke: four cases.* J Emerg Med, 1999. **17**(3): p. 469-71.
439. Rothwell, P.M. and R. Grant, *Cerebral venous sinus thrombosis induced by 'ecstasy'.* J Neurol Neurosurg Psychiatry, 1993. **56**(9): p. 1035.
440. Gledhill, J.A., et al., *Subarachnoid haemorrhage associated with MDMA abuse [letter].* J Neurol Neurosurg Psychiatry, 1993. **56**(9): p. 1036-7.
441. Manchanda, S. and M.J. Connolly, *Cerebral infarction in association with Ecstasy abuse.* Postgrad Med J, 1993. **69**(817): p. 874-5.
442. Selmi, F., et al., *Intracerebral haemorrhage due to amphetamine abuse: report of two cases with underlying arteriovenous malformations.* Br J Neurosurg, 1995. **9**(1): p. 93-6.
443. Ho, M.P., J.L. Tsai, and Y.K. Wong, *Subarachnoid hemorrhage and death following coingestion of MDMA with other drugs.* J Chin Med Assoc, 2004. **67**(12): p. 640-3.
444. Johnson, J., et al., *Posterior spinal artery aneurysm rupture after 'Ecstasy' abuse.* J Neurointerv Surg, 2014.
445. Finley, J.J.t., M.A. Konstam, and J.E. Udelson, *Arginine vasopressin antagonists for the treatment of heart failure and hyponatremia.* Circulation, 2008. **118**(4): p. 410-21.
446. Bolignano, D., et al., *Copeptin (CTproAVP), a new tool for understanding the role of vasopressin in pathophysiology.* Clin Chem Lab Med, 2014. **52**(10): p. 1447-56.

447. Droogmans, S., et al., *Possible association between 3,4-methylenedioxymethamphetamine abuse and valvular heart disease.* Am J Cardiol, 2007. **100**(9): p. 1442-5.
448. Bonsignore, A., et al., *MDMA Induced Cardio-toxicity and Pathological Myocardial Effects: A Systematic Review of Experimental Data and Autopsy Findings.* Cardiovasc Toxicol, 2019. **19**(6): p. 493-499.
449. Aitchison, K.J., et al., *Ecstasy (MDMA)-induced hyponatraemia is associated with genetic variants in CYP2D6 and COMT.* J Psychopharmacol, 2012. **26**(3): p. 408-18.
450. Henry, J.A. and I.R. Hill, *Fatal interaction between ritonavir and MDMA.* Lancet, 1998. **352**(9142): p. 1751-2.
451. Baggott, M., L. Jerome, and R. Stuart, *3,4-Methylenedioxymethamphetamine (MDMA); A review of the English-language scientific and medical literature:* , in *First Edition of Investigator's Brochure for MDMA*. 2001, Multidiscplinary Association for Psychedelic Studies.
452. Brvar, M., et al., *Polydipsia as another mechanism of hyponatremia after 'ecstasy' (3,4 methyldioxymethamphetamine) ingestion.* Eur J Emerg Med, 2004. **11**(5): p. 302-4.
453. Corona, G., et al., *Moderate hyponatremia is associated with increased risk of mortality: evidence from a meta-analysis.* PLoS One, 2013. **8**(12): p. e80451.
454. Wolff, K., et al., *Vasopressin and oxytocin secretion in response to the consumption of ecstasy in a clubbing population.* J Psychopharmacol, 2006. **20**(3): p. 400-10.
455. Ayus, J.C., S.G. Achinger, and A. Arieff, *Brain cell volume regulation in hyponatremia: role of sex, age, vasopressin, and hypoxia.* Am J Physiol Renal Physiol, 2008. **295**(3): p. F619-24.
456. Lien, Y.H. and J.I. Shapiro, *Hyponatremia: clinical diagnosis and management.* Am J Med, 2007. **120**(8): p. 653-8.
457. Stoiser, B., et al., *Copeptin, a fragment of the vasopressin precursor, as a novel predictor of outcome in heart failure.* Eur J Clin Invest, 2006. **36**(11): p. 771-8.
458. Morgenthaler, N.G., *Copeptin: a biomarker of cardiovascular and renal function.* Congest Heart Fail, 2010. **16 Suppl 1**: p. S37-44.
459. Yalta, K., et al., *Copeptin and cardiovascular disease: a review of a novel neurohormone.* Int J Cardiol, 2013. **167**(5): p. 1750-9.
460. McGuire, P.K., H. Cope, and T.A. Fahy, *Diversity of psychopathology associated with use of 3,4-methylenedioxymethamphetamine ('Ecstasy').* Br J Psychiatry, 1994. **165**(3): p. 391-5.
461. Huizink, A.C., et al., *Symptoms of anxiety and depression in childhood and use of MDMA: prospective, population based study.* Bmj, 2006. **332**(7545): p. 825-8.
462. MacInnes, N., S.L. Handley, and G.F. Harding, *Former chronic methylenedioxymethamphetamine (MDMA or ecstasy) users report mild depressive symptoms.* J Psychopharmacol, 2001. **15**(3): p. 181-6.
463. Parrott, A.C., E. Sisk, and J.J. Turner, *Psychobiological problems in heavy 'ecstasy' (MDMA) polydrug users.* Drug Alcohol Depend, 2000. **60**(1): p. 105-10.
464. Sumnall, H.R. and J.C. Cole, *Self-reported depressive symptomatology in community samples of polysubstance misusers who report Ecstasy use: a meta-analysis.* J Psychopharmacol, 2005. **19**(1): p. 84-92.

465. Milani, R.M., et al., *Gender differences in self-reported anxiety, depression, and somatization among ecstasy/MDMA polydrug users, alcohol/tobacco users, and nondrug users.* Addict Behav, 2004. **29**(5): p. 965-71.
466. Sumnall, H.R., G.F. Wagstaff, and J.C. Cole, *Self-reported psychopathology in polydrug users.* J Psychopharmacol, 2004. **18**(1): p. 75-82.
467. Medina, K.L. and P.K. Shear, *Anxiety, depression, and behavioral symptoms of executive dysfunction in ecstasy users: contributions of polydrug use.* Drug Alcohol Depend, 2007. **87**(2-3): p. 303-11.
468. Fisk, J.E., et al., *Modelling the adverse effects associated with ecstasy use.* Addiction, 2011. **106**(4): p. 798-805.
469. Scott, L.A., et al., *The impact of comorbid cannabis and methamphetamine use on mental health among regular ecstasy users.* Addict Behav, 2012. **37**(9): p. 1058-62.
470. Daumann, J., et al., *Self-reported psychopathological symptoms in recreational ecstasy (MDMA) users are mainly associated with regular cannabis use: further evidence from a combined cross-sectional/longitudinal investigation.* Psychopharmacology (Berl), 2004. **173**(3-4): p. 398-404.
471. Rougemont-Bucking, A., et al., *Comparing Mental Health across Distinct Groups of Users of Psychedelics, MDMA, Psychostimulants, and Cannabis.* J Psychoactive Drugs, 2019: p. 1-11.
472. Whitaker-Azmitia, P.M. and T.A. Aronson, *"Ecstasy" (MDMA)-induced panic.* Am J Psychiatry, 1989. **146**(1): p. 119.
473. McCann, U.D. and G.A. Ricaurte, *Lasting neuropsychiatric sequelae of (+-)methylenedioxymethamphetamine ('ecstasy') in recreational users.* J Clin Psychopharmacol, 1991. **11**(5): p. 302-5.
474. Pallanti, S. and D. Mazzi, *MDMA (Ecstasy) precipitation of panic disorder.* Biol Psychiatry, 1992. **32**(1): p. 91-5.
475. McCann, U.D. and G.A. Ricaurte, *MDMA ("ecstasy") and panic disorder: induction by a single dose.* Biol Psychiatry, 1992. **32**(10): p. 950-3.
476. Carlyle, M., et al., *Greater empathy in MDMA users.* J Psychopharmacol, 2019: p. 269881119826594.
477. Allott, K., et al., *Neuroendocrine and subjective responses to pharmacological challenge with citalopram: a controlled study in male and female ecstasy/MDMA users.* J Psychopharmacol, 2008.
478. Wetherell, M.A. and C. Montgomery, *Basal functioning of the hypothalamic-pituitary-adrenal (HPA) axis and psychological distress in recreational ecstasy polydrug users.* Psychopharmacology (Berl), 2014. **231**(7): p. 1365-75.
479. Frokjaer, V.G., et al., *In abstinent MDMA users the cortisol awakening response is off-set but associated with prefrontal serotonin transporter binding as in non-users.* Int J Neuropsychopharmacol, 2014. **17**(8): p. 1119-28.
480. George, A.M., S. Olesen, and R.J. Tait, *Ecstasy use and depression: a 4-year longitudinal study among an Australian general community sample.* Psychopharmacology (Berl), 2013. **229**(4): p. 713-21.
481. Thomasius, R., et al., *Mood, cognition and serotonin transporter availability in current and former ecstasy (MDMA) users: the longitudinal perspective.* J Psychopharmacol, 2006. **20**(2): p. 211-25.

482. Abad, S., et al., *MDMA enhances hippocampal-dependent learning and memory under restrictive conditions, and modifies hippocampal spine density.* Psychopharmacology (Berl), 2014. **231**(5): p. 863-74.
483. Semple, D.M., et al., *Reduced in vivo binding to the serotonin transporter in the cerebral cortex of MDMA ('ecstasy') users.* Br J Psychiatry, 1999. **175**: p. 63-9.
484. Gouzoulis-Mayfrank, E. and J. Daumann, *Neurotoxicity of methylenedioxyamphetamines (MDMA; ecstasy) in humans: how strong is the evidence for persistent brain damage?* Addiction, 2006. **101**(3): p. 348-61.
485. Buchert, R., et al., *A voxel-based PET investigation of the long-term effects of "Ecstasy" consumption on brain serotonin transporters.* Am J Psychiatry, 2004. **161**(7): p. 1181-9.
486. Gouzoulis-Mayfrank, E., et al., *Memory impairment suggests hippocampal dysfunction in abstinent ecstasy users.* Prog Neuropsychopharmacol Biol Psychiatry, 2003. **27**(5): p. 819-27.
487. Halpern, J.H., et al., *Residual neuropsychological effects of illicit 3,4-methylenedioxymethamphetamine (MDMA) in individuals with minimal exposure to other drugs.* Drug Alcohol Depend, 2004. **75**(2): p. 135-47.
488. Thomasius, R., et al., *Mood, cognition and serotonin transporter availability in current and former ecstasy (MDMA) users.* Psychopharmacology (Berl), 2003. **167**(1): p. 85-96.
489. Szigeti, B., et al., *Are ecstasy induced serotonergic alterations overestimated for the majority of users?* J Psychopharmacol, 2018. **32**(7): p. 741-748.
490. Daumann, J., Jr., et al., *Neural mechanisms of working memory in ecstasy (MDMA) users who continue or discontinue ecstasy and amphetamine use: evidence from an 18-month longitudinal functional magnetic resonance imaging study.* Biol Psychiatry, 2004. **56**(5): p. 349-55.
491. Gouzoulis-Mayfrank, E., et al., *Memory performance in polyvalent MDMA (ecstasy) users who continue or discontinue MDMA use.* Drug Alcohol Depend, 2005. **78**(3): p. 317-23.
492. Buchert, R., et al., *Reversibility of ecstasy-induced reduction in serotonin transporter availability in polydrug ecstasy users.* Eur J Nucl Med Mol Imaging, 2006. **33**(2): p. 188-99.
493. Bosch, O.G., et al., *Verbal memory deficits are correlated with prefrontal hypometabolism in (18)FDG PET of recreational MDMA users.* PLoS One, 2013. **8**(4): p. e61234.
494. Taurah, L., C. Chandler, and G. Sanders, *Depression, impulsiveness, sleep, and memory in past and present polydrug users of 3,4-methylenedioxymethamphetamine (MDMA, ecstasy).* Psychopharmacology (Berl), 2014. **231**(4): p. 737-51.
495. Smithies, V., et al., *Dysfunctional overnight memory consolidation in ecstasy users.* J Psychopharmacol, 2014. **28**(8): p. 751-62.
496. Laws, K.R. and J. Kokkalis, *Ecstasy (MDMA) and memory function: a meta-analytic update.* Hum Psychopharmacol, 2007.
497. Zakzanis, K.K., Z. Campbell, and D. Jovanovski, *The neuropsychology of ecstasy (MDMA) use: a quantitative review.* Hum Psychopharmacol, 2007. **22**(7): p. 427-35.
498. Schilt, T., et al., *Cognition in novice ecstasy users with minimal exposure to other drugs: a prospective cohort study.* Arch Gen Psychiatry, 2007. **64**(6): p. 728-36.

499. Jager, G., et al., *Incidental use of ecstasy: no evidence for harmful effects on cognitive brain function in a prospective fMRI study.* Psychopharmacology (Berl), 2007. **193**(3): p. 403-14.
500. White, C., J. Brown, and M. Edwards, *Alterations to global but not local motion processing in long-term ecstasy (MDMA) users.* Psychopharmacology (Berl), 2014.
501. Amoroso, T., *The spurious relationship between ecstasy use and neurocognitive deficits: A Bradford Hill review.* Int J Drug Policy, 2019. **64**: p. 47-53.
502. Bedi, G. and J. Redman, *Metamemory in recreational ecstasy polydrug users: what do self-reports of memory failures mean?* J Psychopharmacol, 2008.
503. Bedi, G. and J. Redman, *Ecstasy use and higher-level cognitive functions: weak effects of ecstasy after control for potential confounds.* Psychol Med, 2008. **38**(9): p. 1319-30.
504. Hanson, K.L. and M. Luciana, *Neurocognitive impairments in MDMA and other drug users: MDMA alone may not be a cognitive risk factor.* J Clin Exp Neuropsychol, 2010. **32**(4): p. 337-49.
505. Raj, V., et al., *MDMA (ecstasy) use is associated with reduced BOLD signal change during semantic recognition in abstinent human polydrug users: a preliminary fMRI study.* J Psychopharmacol, 2010. **24**(2): p. 187-201.
506. Roiser, J.P., R.D. Rogers, and B.J. Sahakian, *Neuropsychological function in ecstasy users: a study controlling for polydrug use.* Psychopharmacology (Berl), 2007. **189**(4): p. 505-16.
507. Roberts, C.A., et al., *Differences in prefrontal blood oxygenation during an acute multitasking stressor in ecstasy polydrug users.* Psychol Med, 2015. **45**(2): p. 395-406.
508. Blagrove, M., et al., *Procedural and declarative memory task performance, and the memory consolidation function of sleep, in recent and abstinent ecstasy/MDMA users.* J Psychopharmacol, 2011. **25**(4): p. 465-77.
509. Kish, S.J., et al., *Decreased cerebral cortical serotonin transporter binding in ecstasy users: a positron emission tomography/[(11)C]DASB and structural brain imaging study.* Brain, 2010. **133**(Pt 6): p. 1779-97.
510. Montgomery, C. and J.E. Fisk, *Ecstasy-related deficits in the updating component of executive processes.* Hum Psychopharmacol, 2008.
511. McCann, U.D., et al., *Sleep deprivation differentially impairs cognitive performance in abstinent methylenedioxymethamphetamine ("ecstasy") users.* J Neurosci, 2009. **29**(44): p. 14050-6.
512. Hadjiefthyvoulou, F., et al., *Everyday and prospective memory deficits in ecstasy/polydrug users.* J Psychopharmacol, 2011. **25**(4): p. 453-64.
513. van Holst, R.J. and T. Schilt, *Drug-related decrease in neuropsychological functions of abstinent drug users.* Curr Drug Abuse Rev, 2011. **4**(1): p. 42-56.
514. Cuyas, E., et al., *The Influence of Genetic and Environmental Factors among MDMA Users in Cognitive Performance.* PLoS One, 2011. **6**(11): p. e27206.
515. Jager, G., et al., *Assessment of cognitive brain function in ecstasy users and contributions of other drugs of abuse: results from an FMRI study.* Neuropsychopharmacology, 2008. **33**(2): p. 247-58.
516. Indlekofer, F., et al., *Reduced memory and attention performance in a population-based sample of young adults with a moderate lifetime use of cannabis, ecstasy and alcohol.* J Psychopharmacol, 2009. **23**(5): p. 495-509.

517. Schilt, T., et al., *Long-term neuropsychological effects of ecstasy in middle-aged ecstasy/polydrug users.* Psychopharmacology (Berl), 2010. **207**(4): p. 583-91.
518. Murphy, P.N., et al., *The effects of 'ecstasy' (MDMA) on visuospatial memory performance: findings from a systematic review with meta-analyses.* Hum Psychopharmacol, 2012. **27**(2): p. 113-38.
519. Wagner, D., et al., *A prospective study of learning, memory, and executive function in new MDMA users.* Addiction, 2013. **108**(1): p. 136-45.
520. Wagner, D., et al., *Learning, Memory, and Executive Function in New MDMA Users: A 2-Year Follow-Up Study.* Front Neurosci, 2015. **9**: p. 445.
521. Price, J.S., P. Shear, and K.M. Lisdahl, *Ecstasy exposure & gender: examining components of verbal memory functioning.* PLoS One, 2014. **9**(12): p. e115645.
522. Kuypers, K.P.C., et al., *Verbal memory impairment in polydrug Ecstasy users: A clinical perspective.* PLoS One, 2016. **11**(2): p. e0149438. .
523. Wareing, M., et al., *Verbal working memory deficits in current and previous users of MDMA.* Hum Psychopharmacol, 2004. **19**(4): p. 225-34.
524. von Geusau, N.A., et al., *Impaired executive function in male MDMA ("ecstasy") users.* Psychopharmacology (Berl), 2004. **175**(3): p. 331-41.
525. Murphy, P.N., et al., *Executive working memory deficits in abstinent ecstasy/MDMA users: a critical review.* Neuropsychobiology, 2009. **60**(3-4): p. 159-75.
526. Hoshi, R., et al., *Neurocognitive function in current and ex-users of ecstasy in comparison to both matched polydrug-using controls and drug-naive controls.* Psychopharmacology (Berl), 2007. **194**(3): p. 371-9.
527. Morgan, M.J., *Recreational use of "ecstasy" (MDMA) is associated with elevated impulsivity.* Neuropsychopharmacology, 1998. **19**(4): p. 252-64.
528. Quednow, B.B., et al., *Elevated impulsivity and impaired decision-making cognition in heavy users of MDMA ("Ecstasy").* Psychopharmacology (Berl), 2007. **189**(4): p. 517-30.
529. Morgan, M.J., et al., *Elevated impulsivity and impaired decision-making in abstinent Ecstasy (MDMA) users compared to polydrug and drug-naive controls.* Neuropsychopharmacology, 2006. **31**(7): p. 1562-73.
530. Schilt, T., et al., *Decision making as a predictor of first ecstasy use: a prospective study.* Psychopharmacology (Berl), 2009. **203**(3): p. 519-27.
531. Pirona, A. and M.J. Morgan, *An investigation of the subacute effects of ecstasy on neuropsychological performance, sleep and mood in regular ecstasy users.* J Psychopharmacol, 2010. **24**(2): p. 175-85.
532. Hanson, K.L., M. Luciana, and K. Sullwold, *Reward-related decision-making deficits and elevated impulsivity among MDMA and other drug users.* Drug Alcohol Depend, 2008. **96**(1-2): p. 99-110.
533. Betzler, F., L. Viohl, and N. Romanczuk-Seiferth, *Decision-making in chronic ecstasy users: a systematic review.* Eur J Neurosci, 2017. **45**(1): p. 34-44.
534. Richard, J., et al., *The Stimulating Nature of Gambling Behaviors: Relationships Between Stimulant Use and Gambling Among Adolescents.* J Gambl Stud, 2019. **35**(1): p. 47-62.
535. Wagner, A.C., et al., *Combining Cognitive-Behavioral Conjoint Therapy for PTSD with 3,4-Methylenedioxymethamphetamine (MDMA): A Case Example.* J Psychoactive Drugs, 2019. **51**(2): p. 166-173.

536. Danforth, A.L., et al., *Reduction in social anxiety after MDMA-assisted psychotherapy with autistic adults: a randomized, double-blind, placebo-controlled pilot study.* Psychopharmacology (Berl), 2018. **235**(11): p. 3137-3148.
537. Wolfson, P., et al., *MDMA-assisted psychotherapy for treatment of anxiety and other psychological distress related to life-threatening illnesses.* Submitted for Publication, 2020.
538. Kirkpatrick, M.G., et al., *MDMA effects consistent across laboratories.* Psychopharmacology (Berl), 2014. **231**(19): p. 3899-905.
539. de la Torre, R., et al., *Pharmacology of MDMA in humans.* Ann N Y Acad Sci, 2000. **914**: p. 225-37.
540. Dumont, G.J. and R.J. Verkes, *A review of acute effects of 3,4-methylenedioxymethamphetamine in healthy volunteers.* J Psychopharmacol, 2006. **20**(2): p. 176-87.
541. Hysek, C.M., et al., *Pharmacokinetic and pharmacodynamic effects of methylphenidate and MDMA administered alone or in combination.* Int J Neuropsychopharmacol, 2014. **17**(3): p. 371-81.
542. Vizeli, P. and M.E. Liechti, *Safety pharmacology of acute MDMA administration in healthy subjects.* J Psychopharmacol, 2017. **31**(5): p. 576-588.
543. Desrosiers, N.A., et al., *Oral fluid and plasma 3,4-methylenedioxymethamphetamine (MDMA) and metabolite correlation after controlled oral MDMA administration.* Anal Bioanal Chem, 2013. **405**(12): p. 4067-76.
544. de la Torre, R., et al., *Clinical pharmacokinetics of amfetamine and related substances: monitoring in conventional and non-conventional matrices.* Clin Pharmacokinet, 2004. **43**(3): p. 157-85.
545. de Boer, D., et al., *Gas chromatographic/mass spectrometric assay for profiling the enantiomers of 3,4-methylenedioxymethamphetamine and its chiral metabolites using positive chemical ionization ion trap mass spectrometry.* J Mass Spectrom, 1997. **32**(11): p. 1236-46.
546. Helmlin, H.J., et al., *Analysis of 3,4-methylenedioxymethamphetamine (MDMA) and its metabolites in plasma and urine by HPLC-DAD and GC-MS.* J Anal Toxicol, 1996. **20**(6): p. 432-40.
547. Lanz, M., R. Brenneisen, and W. Thormann, *Enantioselective determination of 3,4-methylene-dioxymethamphetamine and two of its metabolites in human urine by cyclodextrin-modified capillary zone electrophoresis.* Electrophoresis, 1997. **18**(6): p. 1035-43.
548. Ortuno, J., et al., *Quantification of 3,4-methylenedioxymetamphetamine and its metabolites in plasma and urine by gas chromatography with nitrogen-phosphorus detection.* J Chromatogr B Biomed Sci Appl, 1999. **723**(1-2): p. 221-32.
549. Helmlin, H.J. and R. Brenneisen, *Determination of psychotropic phenylalkylamine derivatives in biological matrices by high-performance liquid chromatography with photodiode-array detection.* J Chromatogr, 1992. **593**(1-2): p. 87-94.
550. Yang, J., et al., *Implications of mechanism-based inhibition of CYP2D6 for the pharmacokinetics and toxicity of MDMA.* J Psychopharmacol, 2006. **20**(6): p. 842-9.

551. O'Mathuna, B., et al., *The consequences of 3,4-methylenedioxymethamphetamine induced CYP2D6 inhibition in humans.* J Clin Psychopharmacol, 2008. **28**(5): p. 523-9.
552. Yubero-Lahoz, S., et al., *Sex Differences in 3,4-Methylenedioxymethamphetamine (MDMA; Ecstasy)-Induced Cytochrome P450 2D6 Inhibition in Humans.* Clin Pharmacokinet, 2011. **50**(5): p. 319-29.
553. Yubero-Lahoz, S., et al., *Changes in CYP1A2 activity in humans after 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) administration using caffeine as a probe drug.* Drug Metab Pharmacokinet, 2012. **27**(6): p. 605-13.
554. Fallon, J.K., et al., *Stereospecific analysis and enantiomeric disposition of 3, 4-methylenedioxymethamphetamine (Ecstasy) in humans [published erratum appears in Clin Chem 1999 Sep;45(9):1585].* Clin Chem, 1999. **45**(7): p. 1058-69.
555. Schwaninger, A.E., et al., *Urinary excretion kinetics of 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) and its phase I and phase II metabolites in humans following controlled MDMA administration.* Clin Chem, 2011. **57**(12): p. 1748-56.
556. Steuer, A.E., et al., *Impact of Cytochrome P450 2D6 Function on the Chiral Blood Plasma Pharmacokinetics of 3,4-Methylenedioxymethamphetamine (MDMA) and Its Phase I and II Metabolites in Humans.* PLoS One, 2016. **11**(3): p. e0150955.
557. Farre, M., et al., *Human pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) after repeated doses taken 4 h apart Human pharmacology of MDMA after repeated doses taken 4 h apart.* Eur Neuropsychopharmacol, 2015. **25**(10): p. 1637-49.
558. Ramamoorthy, S. and R.D. Blakely, *Phosphorylation and sequestration of serotonin transporters differentially modulated by psychostimulants.* Science, 1999. **285**(5428): p. 763-766.
559. Farre, M., et al., *Repeated doses administration of MDMA in humans: pharmacological effects and pharmacokinetics.* Psychopharmacology (Berl), 2004. **173**(3-4): p. 364-75.
560. Pizarro, N., et al., *Stereochemical analysis of 3,4-methylenedioxymethamphetamine and its main metabolites in human samples including the catechol-type metabolite (3,4-dihydroxymethamphetamine).* Drug Metab Dispos, 2004. **32**(9): p. 1001-7.
561. Pizarro, N., et al., *Stereochemical analysis of 3,4-methylenedioxymethamphetamine and its main metabolites by gas chromatography/mass spectrometry.* Rapid Commun Mass Spectrom, 2003. **17**(4): p. 330-6.
562. Pizarro, N., et al., *Determination of MDMA and its metabolites in blood and urine by gas chromatography-mass spectrometry and analysis of enantiomers by capillary electrophoresis.* J Anal Toxicol, 2002. **26**(3): p. 157-65.
563. Segura, M., et al., *3,4-Dihydroxymethamphetamine (HHMA). A Major in Vivo 3,4- methylenedioxymethamphetamine (MDMA) Metabolite in Humans.* Chem Res Toxicol, 2001. **14**(9): p. 1203-1208.
564. Steuer, A.E., et al., *Development and validation of an LC-MS/MS method after chiral derivatization for the simultaneous stereoselective determination of*

methylenedioxy-methamphetamine (MDMA) and its phase I and II metabolites in human blood plasma. Drug Test Anal, 2015. **7**(7): p. 592-602.
565. Steuer, A.E., et al., *Chiral Plasma Pharmacokinetics of 3,4-Methylenedioxymethamphetamine and its Phase I and II Metabolites following Controlled Administration to Humans.* Drug Metab Dispos, 2015. **43**(12): p. 1864-71.
566. de la Torre, R., et al., *Human pharmacology of MDMA: pharmacokinetics, metabolism, and disposition.* Ther Drug Monit, 2004. **26**(2): p. 137-44.
567. Abraham, T.T., et al., *Urinary MDMA, MDA, HMMA, and HMA excretion following controlled MDMA administration to humans.* J Anal Toxicol, 2009. **33**(8): p. 439-46.
568. Vizeli, P., et al., *Pharmacogenetics of ecstasy: CYP1A2, CYP2C19, and CYP2B6 polymorphisms moderate pharmacokinetics of MDMA in healthy subjects.* Eur Neuropsychopharmacol, 2017. **27**(3): p. 232-238.
569. Rodgers, J.T., et al., *Kinetic mechanism of time-dependent inhibition of CYP2D6 by 3,4-methylenedioxymethamphetamine (MDMA): functional heterogeneity of the enzyme and the reversibility of its inactivation.* Biochem Pharmacol, 2018.
570. Pardo-Lozano, R., et al., *Clinical Pharmacology of 3,4-Methylenedioxymethamphetamine (MDMA, "Ecstasy"): The Influence of Gender and Genetics (CYP2D6, COMT, 5-HTT).* PLoS One, 2012. **7**(10): p. e47599.
571. Vizeli, P., H.E. Meyer Zu Schwabedissen, and M.E. Liechti, *Role of serotonin transporter and receptor gene variations in the acute effects of MDMA in healthy subjects.* ACS Chem Neurosci, 2018.
572. Vizeli, P. and M.E. Liechti, *Oxytocin receptor gene variations and socio-emotional effects of MDMA: A pooled analysis of controlled studies in healthy subjects.* PLoS One, 2018. **13**(6): p. e0199384.
573. Segura, M., et al., *Contribution of cytochrome P450 2D6 to 3,4-methylenedioxymethamphetamine disposition in humans: use of paroxetine as a metabolic inhibitor probe.* Clin Pharmacokinet, 2005. **44**(6): p. 649-60.
574. Schmid, Y., et al., *Interactions between bupropion and 3,4-methylenedioxymethamphetamine in healthy subjects.* J Pharmacol Exp Ther, 2015. **353**(1): p. 102-11.
575. Steuer, A.E., et al., *Inhibition potential of 3,4-methylenedioxymethamphetamine (MDMA) and its metabolites on the in vitro monoamine oxidase (MAO)-catalyzed deamination of the neurotransmitters serotonin and dopamine.* Toxicol Lett, 2016. **243**: p. 48-55.
576. Liechti, M.E., et al., *Acute psychological effects of 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") are attenuated by the serotonin uptake inhibitor citalopram.* Neuropsychopharmacology, 2000. **22**(5): p. 513-21.
577. Liechti, M.E. and F.X. Vollenweider, *The serotonin uptake inhibitor citalopram reduces acute cardiovascular and vegetative effects of 3,4-methylenedioxymethamphetamine ('Ecstasy') in healthy volunteers.* J Psychopharmacol, 2000. **14**(3): p. 269-74.
578. Pacifici, R., et al., *Paroxetine inhibits acute effects of 3,4-methylenedioxymethamphetamine on the immune system in humans.* J Pharmacol Exp Ther, 2004. **309**(1): p. 285-92.

579. Tancer, M. and C.E. Johanson, *The effects of fluoxetine on the subjective and physiological effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans.* Psychopharmacology (Berl), 2007. **189**(4): p. 565-73.
580. Liechti, M.E., et al., *Psychological and physiological effects of MDMA ("Ecstasy") after pretreatment with the 5-HT(2) antagonist ketanserin in healthy humans.* Neuropsychopharmacology, 2000. **23**(4): p. 396-404.
581. Dipasquale, O., et al., *Receptor-Enriched Analysis of functional connectivity by targets (REACT): A novel, multimodal analytical approach informed by PET to study the pharmacodynamic response of the brain under MDMA.* Neuroimage, 2019.
582. Hysek, C.M., et al., *The norepinephrine transporter inhibitor reboxetine reduces stimulant effects of MDMA ("ecstasy") in humans.* Clin Pharmacol Ther, 2011. **90**(2): p. 246-55.
583. Simmler, L.D., C.M. Hysek, and M.E. Liechti, *Sex differences in the effects of MDMA (ecstasy) on plasma copeptin in healthy subjects.* J Clin Endocrinol Metab, 2011. **96**(9): p. 2844-50.
584. Holze, F., et al., *Distinct acute effects of LSD, MDMA, and D-amphetamine in healthy subjects.* Neuropsychopharmacology, 2020. **45**(3): p. 462-471.
585. Moron, J.A., et al., *Dopamine uptake through the norepinephrine transporter in brain regions with low levels of the dopamine transporter: evidence from knock-out mouse lines.* J Neurosci, 2002. **22**(2): p. 389-95.
586. Liechti, M.E. and F.X. Vollenweider, *Acute psychological and physiological effects of MDMA ("Ecstasy") after haloperidol pretreatment in healthy humans.* Eur Neuropsychopharmacol, 2000. **10**(4): p. 289-95.
587. Schmid, Y., et al., *Differential effects of MDMA and methylphenidate on social cognition.* J Psychopharmacol, 2014. **28**(9): p. 847-56.
588. Bershad, A.K., et al., *Effects of acute doses of prosocial drugs methamphetamine and alcohol on plasma oxytocin levels.* J Clin Psychopharmacol, 2015. **35**(3): p. 308-12.
589. Kirkpatrick, M.G., et al., *Plasma oxytocin concentrations following MDMA or intranasal oxytocin in humans.* Psychoneuroendocrinology, 2014. **46**: p. 23-31.
590. Kuypers, K.P., et al., *Multifaceted empathy of healthy volunteers after single doses of MDMA: A pooled sample of placebo-controlled studies.* J Psychopharmacol, 2017. **31**(5): p. 589-598.
591. Kuypers, K.P., et al., *No Evidence that MDMA-Induced Enhancement of Emotional Empathy Is Related to Peripheral Oxytocin Levels or 5-HT1a Receptor Activation.* PLoS One, 2014. **9**(6): p. e100719.
592. Boxler, M.I., et al., *Human Metabolome Changes after a Single Dose of 3,4-Methylenedioxymethamphetamine (MDMA) with Special Focus on Steroid Metabolism and Inflammation Processes.* J Proteome Res, 2018. **17**(8): p. 2900-2907.
593. Grob, C., *Unpublished data on human study of psychological and physiological effects of MDMA.* 2001.
594. Kuypers, K.P., et al., *Inhibition of MDMA-induced increase in cortisol does not prevent acute impairment of verbal memory.* Br J Pharmacol, 2013. **168**(3): p. 607-17.

595. Seibert, J., et al., *Acute effects of 3,4-methylenedioxymethamphetamine and methylphenidate on circulating steroid levels in healthy subjects.* Neuroendocrinology, 2014. **100**(1): p. 17-25.
596. Pacifici, R., et al., *Cell-mediated immune response in MDMA users after repeated dose administration: studies in controlled versus noncontrolled settings.* Ann N Y Acad Sci, 2002. **965**: p. 421-33.
597. Bershad, A.K., M.A. Miller, and H. de Wit, *MDMA does not alter responses to the Trier Social Stress Test in humans.* Psychopharmacology (Berl), 2017. **234**(14): p. 2159-2166.
598. Walpola, I.C., et al., *Altered Insula Connectivity under MDMA.* Neuropsychopharmacology, 2017. **42**(11): p. 2152-2162.
599. Gamma, A., et al., *3,4-Methylenedioxymethamphetamine (MDMA) modulates cortical and limbic brain activity as measured by [H(2)(15)O]-PET in healthy humans.* Neuropsychopharmacology, 2000. **23**(4): p. 388-95.
600. Phelps, E.A., et al., *Activation of the left amygdala to a cognitive representation of fear.* Nat Neurosci, 2001. **4**(4): p. 437-41.
601. Ramaekers, J.G., et al., *Involvement of inferior parietal lobules in prospective memory impairment during acute MDMA (ecstasy) intoxication: an event-related fMRI study.* Neuropsychopharmacology, 2009. **34**(7): p. 1641-8.
602. Kuypers, K.P., et al., *MDMA intoxication and verbal memory performance: a placebo-controlled pharmaco-MRI study.* J Psychopharmacol, 2011. **25**(8): p. 1053-61.
603. Carhart-Harris, R.L., et al., *The Effects of Acutely Administered 3,4-Methylenedioxymethamphetamine on Spontaneous Brain Function in Healthy Volunteers Measured with Arterial Spin Labeling and Blood Oxygen Level-Dependent Resting State Functional Connectivity.* Biol Psychiatry, 2015. **78**(8): p. 554-62.
604. Bosker, W.M., et al., *Dose-related effects of MDMA on psychomotor function and mood before, during, and after a night of sleep loss.* Psychopharmacology (Berl), 2010. **209**(1): p. 69-76.
605. Wagner, M.T., et al., *Therapeutic effect of increased openness: Investigating mechanism of action in MDMA-assisted psychotherapy.* J Psychopharmacol, 2017. **31**(8): p. 967-974.
606. Erritzoe, D., et al., *Effects of psilocybin therapy on personality structure.* Acta Psychiatr Scand, 2018. **138**(5): p. 368-378.
607. Maclean, K.A., M.W. Johnson, and R.R. Griffiths, *Mystical experiences occasioned by the hallucinogen psilocybin lead to increases in the personality domain of openness.* J Psychopharmacol, 2011. **25**(11): p. 1453-61.
608. Baggott, M.J., et al., *3,4-Methylenedioxymethamphetamine (MDMA, 'Ecstasy') and Prazosin Interactions in Humans.*, in *70th Annual Meeting of the College on Problems of Drug Dependence*. 2008: San Juan, Puerto Rico.
609. Kuypers, K.P.C., et al., *MDMA-induced indifference to negative sounds is mediated by the 5-HT2A receptor.* Psychopharmacology (Berl), 2018. **235**(2): p. 481-490.
610. Gabay, A.S., et al., *MDMA Increases Cooperation and Recruitment of Social Brain Areas When Playing Trustworthy Players in an Iterated Prisoner's Dilemma.* J Neurosci, 2019. **39**(2): p. 307-320.

611. Schmidt, A., et al., *Acute Effects of Methylphenidate, Modafinil, and MDMA on Negative Emotion Processing.* Int J Neuropsychopharmacol, 2018. **21**(4): p. 345-354.
612. Kirkpatrick, M.G. and H. de Wit, *MDMA: a social drug in a social context.* Psychopharmacology (Berl), 2015. **232**(6): p. 1155-63.
613. Kirkpatrick, M., et al., *Prosocial effects of MDMA: A measure of generosity.* J Psychopharmacol, 2015. **29**(6): p. 661-8.
614. Frye, C.G., et al., *MDMA decreases the effects of simulated social rejection.* Pharmacol Biochem Behav, 2014. **117**: p. 1-6.
615. Tancer, M.E. and C.E. Johanson, *The subjective effects of MDMA and mCPP in moderate MDMA users.* Drug Alcohol Depend, 2001. **65**(1): p. 97-101.
616. Baggott, M.J., et al., *Intimate insight: MDMA changes how people talk about significant others.* J Psychopharmacol, 2015. **29**(6): p. 669-77.
617. Corey, V.R., V.D. Pisano, and J.H. Halpern, *Effects of 3,4-Methylenedioxymethamphetamine on Patient Utterances in a Psychotherapeutic Setting.* J Nerv Ment Dis, 2016.
618. Lamers, C.T., et al., *Dissociable effects of a single dose of ecstasy (MDMA) on psychomotor skills and attentional performance.* J Psychopharmacol, 2003. **17**(4): p. 379-87.
619. Spronk, D.B., et al., *The acute effects of MDMA and ethanol administration on electrophysiological correlates of performance monitoring in healthy volunteers.* Psychopharmacology (Berl), 2014. **231**(14): p. 2877-88.
620. Bosker, W.M., et al., *MDMA (ecstasy) effects on actual driving performance before and after sleep deprivation, as function of dose and concentration in blood and oral fluid.* Psychopharmacology (Berl), 2012. **222**(3): p. 367-76.
621. Kuypers, K.P. and J.G. Ramaekers, *Transient memory impairment after acute dose of 75mg 3.4-Methylene-dioxymethamphetamine.* J Psychopharmacol, 2005. **19**(6): p. 633-9.
622. Ramaekers, J.G. and K.P. Kuypers, *Acute effects of 3,4-methylenedioxymethamphetamine (MDMA) on behavioral measures of impulsivity: alone and in combination with alcohol.* Neuropsychopharmacology, 2006. **31**(5): p. 1048-55.
623. Kuypers, K.P., N. Samyn, and J.G. Ramaekers, *MDMA and alcohol effects, combined and alone, on objective and subjective measures of actual driving performance and psychomotor function.* Psychopharmacology (Berl), 2006. **187**(4): p. 467-75.
624. Kuypers, K.P. and J.G. Ramaekers, *Acute dose of MDMA (75 mg) impairs spatial memory for location but leaves contextual processing of visuospatial information unaffected.* Psychopharmacology (Berl), 2007. **189**(4): p. 557-63.
625. Ramaekers, J.G., K.P. Kuypers, and N. Samyn, *Stimulant effects of 3,4-methylenedioxymethamphetamine (MDMA) 75 mg and methylphenidate 20 mg on actual driving during intoxication and withdrawal.* Addiction, 2006. **101**(11): p. 1614-21.
626. Clark, C.M., et al., *Acute effects of MDMA on autonomic cardiac activity and their relation to subjective prosocial and stimulant effects.* Psychophysiology, 2015. **52**(3): p. 429-35.
627. Pacifici, R., et al., *Immunomodulating activity of MDMA.* Ann N Y Acad Sci, 2000. **914**: p. 215-24.

628. Pacifici, R., et al., *Immunomodulating properties of MDMA alone and in combination with alcohol: a pilot study.* Life Sci, 1999. **65**(26): p. L309-16.
629. Pacifici, R., et al., *Acute effects of 3,4-methylenedioxymethamphetamine alone and in combination with ethanol on the immune system in humans.* J Pharmacol Exp Ther, 2001. **296**(1): p. 207-15.
630. Pacifici, R., et al., *Effects of repeated doses of MDMA ("ecstasy") on cell-mediated immune response in humans.* Life Sci, 2001. **69**(24): p. 2931-41.
631. McElhatton, P.R., et al., *Congenital anomalies after prenatal ecstasy exposure [letter]*. Lancet, 1999. **354**(9188): p. 1441-2.
632. Bateman, D.N., et al., *A case control study to examine the pharmacological factors underlying ventricular septal defects in the North of England.* Eur J Clin Pharmacol, 2004. **60**(9): p. 635-41.
633. Ho, E., L. Karimi-Tabesh, and G. Koren, *Characteristics of pregnant women who use Ecstasy (3, 4- methylenedioxymethamphetamine).* Neurotoxicol Teratol, 2001. **23**(6): p. 561-7.
634. Singer, L.T., et al., *Neurobehavioral outcomes of infants exposed to MDMA (Ecstasy) and other recreational drugs during pregnancy.* Neurotoxicol Teratol, 2012. **34**(3): p. 303-10.
635. Singer, L.T., et al., *Motor delays in MDMA (ecstasy) exposed infants persist to 2years.* Neurotoxicol Teratol, 2016.
636. Huxster, J.K., A. Pirona, and M.J. Morgan, *The sub-acute effects of recreational ecstasy (MDMA) use: a controlled study in humans.* J Psychopharmacol, 2006. **20**(2): p. 281-90.
637. Neff, K., *The Development and validation of a scale to measure self-compassion.* Self and Identity, 2003. **2**: p. 223-250.
638. Blake, D.D., et al., *A clinician rating scale for assessing current and lifetime PTSD: the CAPS-1*. . Behav Ther, 1990. **13**: p. 187-188.
639. Nagy, L.M., et al., *Open prospective trial of fluoxetine for posttraumatic stress disorder.* J Clin Psychopharmacol, 1993. **13**(2): p. 107-13.
640. Weathers, F.W., *Clinician-Administered PTSD Scale (CAPS): Technical Manual*. 2004, Los Angeles, CA: Western Psychological Services.
641. Hexel, M. and G. Sonneck, *Somatoform symptoms, anxiety, and depression in the context of traumatic life experiences by comparing participants with and without psychiatric diagnoses.* Psychopathology, 2002. **35**(5): p. 303-12.
642. Afari, N., et al., *Psychological trauma and functional somatic syndromes: a systematic review and meta-analysis.* Psychosom Med, 2014. **76**(1): p. 2-1.
643. Pietrzak, R.H., et al., *Psychiatric comorbidity of full and partial posttraumatic stress disorder among older adults in the United States: results from wave 2 of the National Epidemiologic Survey on Alcohol and Related Conditions.* Am J Geriatr Psychiatry, 2012. **20**(5): p. 380-90.
644. Baker, D.G., et al., *Relationship between posttraumatic stress disorder and self-reported physical symptoms in Persian Gulf War veterans.* Arch Intern Med, 1997. **157**(18): p. 2076-8.
645. Hoge, C.W., et al., *Association of posttraumatic stress disorder with somatic symptoms, health care visits, and absenteeism among Iraq war veterans.* Am J Psychiatry, 2007. **164**(1): p. 150-3.
646. Gouzoulis-Mayfrank, E., et al., *Psychopathological, neuroendocrine and autonomic effects of 3,4-methylenedioxyethylamphetamine (MDE), psilocybin and*

d-methamphetamine in healthy volunteers. Results of an experimental double-blind placebo-controlled study. Psychopharmacology (Berl), 1999. **142**(1): p. 41-50.

647. Song, H., et al., *Stress related disorders and subsequent risk of life threatening infections: population based sibling controlled cohort study.* BMJ, 2019. **367**: p. l5784.
648. Jiang, X., et al., *Stress Impairs 5-HT(2A) Receptor-Mediated Serotonergic Facilitation of GABA Release in Juvenile Rat Basolateral Amygdala.* Neuropsychopharmacology, 2009. **34**(2): p. 410-23.
649. Gradus, J.L., et al., *Posttraumatic stress disorder and completed suicide.* Am J Epidemiol, 2010. **171**(6): p. 721-7.
650. Conner, K.R., et al., *Posttraumatic stress disorder and suicide in 5.9 million individuals receiving care in the veterans health administration health system.* J Affect Disord, 2014. **166**: p. 1-5.
651. US Food and Drug Administration, *Guidance for industry: suicidal ideation and behavior: prospective assessment of occurrence in clinical trials.* Silver Springs, MD: US Food and Drug Administration Available at: h ttp://www. fda. gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm315156. htm. Accessed October, 2012. **5**: p. 2012.
652. Nilsson, M.E., et al., *Columbia Suicide Severity Rating Scale Scoring and Data Analysis Guide*, in *CSSRS Scoring Version 2.0*. 2013: http://www.cssrs.columbia.edu/documents/ScoringandDataAnalysisGuide_Feb2013.pdf. p. 1-13.
653. Stone, T.E., C. Swanson, and M.D. Feldman, *Venlafaxine discontinuation syndrome and suicidal ideation: a case series.* J Clin Psychopharmacol, 2007. **27**(1): p. 94-5.
654. Tint, A., P.M. Haddad, and I.M. Anderson, *The effect of rate of antidepressant tapering on the incidence of discontinuation symptoms: a randomised study.* J Psychopharmacol, 2008. **22**(3): p. 330-2.
655. Valuck, R.J., H.D. Orton, and A.M. Libby, *Antidepressant discontinuation and risk of suicide attempt: a retrospective, nested case-control study.* J Clin Psychiatry, 2009. **70**(8): p. 1069-77.
656. Young, M.B., et al., *Inhibition of serotonin transporters disrupts the enhancement of fear memory extinction by 3,4-methylenedioxymethamphetamine (MDMA).* Psychopharmacology (Berl), 2017.
657. Feduccia, A.A. and M.C. Mithoefer, *MDMA-assisted psychotherapy for PTSD: Are memory reconsolidation and fear extinction underlying mechanisms?* Prog Neuropsychopharmacol Biol Psychiatry, 2018. **84**(Pt A): p. 221-228.
658. Randolph, C., et al., *The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity.* J Clin Exp Neuropsychol, 1998. **20**(3): p. 310-9.
659. Gronwall, D.M., *Paced auditory serial-addition task: a measure of recovery from concussion.* Percept Mot Skills, 1977. **44**(2): p. 367-73.
660. Roman, D.D., et al., *Extended norms for the paced auditory serial addition task.* . Clin Neuropsychol, 1991. **5**(1): p. 33-40.
661. Kamilar-Britt, P. and G. Bedi, *The prosocial effects of 3,4-methylenedioxymethamphetamine (MDMA): Controlled studies in humans and laboratory animals.* Neurosci Biobehav Rev, 2015. **57**: p. 433-46.

662. Bershad, A.K., et al., *The effects of MDMA on socio-emotional processing: Does MDMA differ from other stimulants?* J Psychopharmacol, 2016. **30**(12): p. 1248-1258.
663. Dumont, G.J., et al., *Cannabis coadministration potentiates the effects of "ecstasy" on heart rate and temperature in humans.* Clin Pharmacol Ther, 2009. **86**(2): p. 160-6.
664. Hysek, C.M., et al., *alpha(1)-Adrenergic receptors contribute to the acute effects of 3,4-methylenedioxymethamphetamine in humans.* J Clin Psychopharmacol, 2013. **33**(5): p. 658-66.
665. Johanson, C.E., et al., *Discriminative stimulus effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans trained to discriminate among d-amphetamine, meta-chlorophenylpiperazine and placebo.* Drug Alcohol Depend, 2006. **81**(1): p. 27-36.
666. Schmid, Y., et al., *Effects of methylphenidate and MDMA on appraisal of erotic stimuli and intimate relationships.* Eur Neuropsychopharmacol, 2015. **25**(1): p. 17-25.
667. Marrone, G.F., et al., *Amphetamine analogs methamphetamine and 3,4-methylenedioxymethamphetamine (MDMA) differentially affect speech.* Psychopharmacology (Berl), 2010. **208**(2): p. 169-77.
668. Davis, A.K. and H. Rosenberg, *The prevalence, intensity, and assessment of craving for MDMA/ecstasy in recreational users.* J Psychoactive Drugs, 2014. **46**(2): p. 154-61.
669. Degenhardt, L., R. Bruno, and L. Topp, *Is ecstasy a drug of dependence?* Drug Alcohol Depend, 2010. **107**(1): p. 1-10.
670. Cottler, L.B., et al., *Ecstasy abuse and dependence among adolescents and young adults: applicability and reliability of DSM-IV criteria.* Hum Psychopharmacol, 2001. **16**(8): p. 599-606.
671. Topp, L., et al., *Ecstasy use in Australia: patterns of use and associated harm.* Drug Alcohol Depend, 1999. **55**(1-2): p. 105-15.
672. Verheyden, S.L., J.A. Henry, and H.V. Curran, *Acute, sub-acute and long-term subjective consequences of 'ecstasy' (MDMA) consumption in 430 regular users.* Hum Psychopharmacol, 2003. **18**(7): p. 507-17.
673. Meyer, J.S., *3,4-methylenedioxymethamphetamine (MDMA): current perspectives.* Subst Abuse Rehabil, 2013. **4**: p. 83-99.
674. Cottler, L.B., K.S. Leung, and A.B. Abdallah, *Test-re-test reliability of DSM-IV adopted criteria for 3,4-methylenedioxymethamphetamine (MDMA) abuse and dependence: a cross-national study.* Addiction, 2009. **104**(10): p. 1679-90.
675. Topp L.J., H. W.D.., and H. J., *Is there a dependence syndrome for ecstasy?* 1997, Randwick, NSW: National Drug & Alcohol Research Centre.
676. von Sydow, K., et al., *Use, abuse and dependence of ecstasy and related drugs in adolescents and young adults-a transient phenomenon? Results from a longitudinal community study.* Drug Alcohol Depend, 2002. **66**(2): p. 147-59.
677. Powers, W.J., et al., *Guidelines for the early management of patients With acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association.* Stroke, 2019. **50**(12): p. e344-e418.

678. McCann, U.D. and G.A. Ricaurte, *Caveat emptor: editors beware.* Neuropsychopharmacology, 2001. **24**(3): p. 333-6.
679. Searchfield, G.D., et al., *A proof-of-principle study of the short-term effects of 3,4-methylenedioxymethamphetamine (MDMA) on tinnitus and neural connectivity.* Int J Neurosci, 2020: p. 1-12.
680. Sessa, B., et al., *First study of safety and tolerability of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy in patients with alcohol use disorder: preliminary data on the first four participants.* BMJ Case Rep, 2019. **12**(7).
681. de Wit, H. and A.K. Bershad, *MDMA enhances pleasantness of affective touch.* Neuropsychopharmacology, 2020. **45**(1): p. 217-239.
682. Bershad, A.K., et al., *Effects of MDMA on attention to positive social cues and pleasantness of affective touch.* Neuropsychopharmacology, 2019. **44**(10): p. 1698-1705.
683. Gabay, A.S., et al., *Psilocybin and MDMA reduce costly punishment in the Ultimatum Game.* Sci Rep, 2018. **8**(1): p. 8236.
684. Borissova, A., et al., *Acute effects of MDMA on trust, cooperative behaviour and empathy: A double-blind, placebo-controlled experiment.* J Psychopharmacol, 2020: p. 269881120926673.
685. Roseman, L., et al., *The effects of psilocybin and MDMA on between-network resting state functional connectivity in healthy volunteers.* Front Hum Neurosci, 2014. **8**: p. 204.
686. Dolder, P.C., et al., *Direct comparison of the acute subjective, emotional, autonomic, and endocrine effects of MDMA, methylphenidate, and modafinil in healthy subjects.* Psychopharmacology (Berl), 2018. **235**(2): p. 467-479.
687. Schmidt, A., et al., *Comparative Effects of Methylphenidate, Modafinil, and MDMA on Response Inhibition Neural Networks in Healthy Subjects.* Int J Neuropsychopharmacol, 2017. **20**(9): p. 712-720.
688. Boxler, M.I., et al., *First Time View on Human Metabolome Changes after a Single Intake of 3,4-Methylenedioxymethamphetamine in Healthy Placebo-Controlled Subjects.* J Proteome Res, 2017. **16**(9): p. 3310-3320.
689. van Heugten-Van der Kloet, D., et al., *MDMA, cannabis, and cocaine produce acute dissociative symptoms.* Psychiatry Res, 2015. **228**(3): p. 907-12.
690. Kuypers, K.P., M. Wingen, and J.G. Ramaekers, *Memory and mood during the night and in the morning after repeated evening doses of MDMA.* J Psychopharmacol, 2008. **22**(8): p. 895-903.
691. Kuypers, K.P., et al., *Acute effects of nocturnal doses of MDMA on measures of impulsivity and psychomotor performance throughout the night.* Psychopharmacology (Berl), 2007. **192**(1): p. 111-9.
692. de Sousa Fernandes Perna, E.B., et al., *Memory and mood during MDMA intoxication, with and without memantine pretreatment.* Neuropharmacology, 2014. **87**: p. 198-205.
693. Haijen, E., et al., *Peripheral endocannabinoid concentrations are not associated with verbal memory impairment during MDMA intoxication.* Psychopharmacology (Berl), 2018. **235**(3): p. 709-717.
694. Baggott, M.J., et al., *Effects of 3,4-methylenedioxymethamphetamine on socioemotional feelings, authenticity, and autobiographical disclosure in healthy volunteers in a controlled setting.* J Psychopharmacol, 2016. **30**(4): p. 378-87.

695. Francis, S.M., et al., *Urinary and plasma oxytocin changes in response to MDMA or intranasal oxytocin administration.* Psychoneuroendocrinology, 2016. **74**: p. 92-100.
696. Agurto, C., et al., *Detection of acute 3,4-methylenedioxymethamphetamine (MDMA) effects across protocols using automated natural language processing.* Neuropsychopharmacology, 2020. **45**(5): p. 823-832.
697. Doss, M.K., et al., *MDMA Impairs Both the Encoding and Retrieval of Emotional Recollections.* Neuropsychopharmacology, 2018. **43**(4): p. 791-800.
698. Papaseit, E., et al., *Human Pharmacology of Mephedrone in Comparison with MDMA.* Neuropsychopharmacology, 2016. **41**(11): p. 2704-13.
699. de la Torre, R., et al., *MDMA (ecstasy) pharmacokinetics in a CYP2D6 poor metaboliser and in nine CYP2D6 extensive metabolisers.* Eur J Clin Pharmacol, 2005. **61**(7): p. 551-4.
700. Hernandez-Lopez, C., et al., *3,4-Methylenedioxymethamphetamine (ecstasy) and alcohol interactions in humans: psychomotor performance, subjective effects, and pharmacokinetics.* J Pharmacol Exp Ther, 2002. **300**(1): p. 236-44.
701. Lansbergen, M.M., et al., *Acute effects of MDMA (3,4-methylenedioxymethamphetamine) on EEG oscillations: alone and in combination with ethanol or THC (delta-9-tetrahydrocannabinol).* Psychopharmacology (Berl), 2011. **213**(4): p. 745-56.
702. Dumont, G.J., et al., *Acute psychomotor effects of MDMA and ethanol (co-) administration over time in healthy volunteers.* J Psychopharmacol, 2010. **24**(2): p. 155-64.
703. Dumont, G.J., et al., *Acute neuropsychological effects of MDMA and ethanol (co-)administration in healthy volunteers.* Psychopharmacology (Berl), 2008. **197**(3): p. 465-74.
704. Dumont, G.J., et al., *Ethanol co-administration moderates 3,4-methylenedioxymethamphetamine effects on human physiology.* J Psychopharmacol, 2010. **24**(2): p. 165-74.
705. Samyn, N., et al., *Plasma, oral fluid and sweat wipe ecstasy concentrations in controlled and real life conditions.* Forensic Sci Int, 2002. **128**(1-2): p. 90.
706. Veldstra, J.L., et al., *Effects of alcohol (BAC 0.5 per thousand) and ecstasy (MDMA 100 mg) on simulated driving performance and traffic safety.* Psychopharmacology (Berl), 2012. **222**(3): p. 377-90.
707. Parrott, A.C., et al., *MDMA and methamphetamine: some paradoxical negative and positive mood changes in an acute dose laboratory study.* Psychopharmacology (Berl), 2011.
708. Stough, C., et al., *The acute effects of 3,4-methylenedioxymethamphetamine and d-methamphetamine on human cognitive functioning.* Psychopharmacology (Berl), 2012. **220**(4): p. 799-807.
709. Stough, C., et al., *The acute effects of 3,4-methylenedioxymethamphetamine and methamphetamine on driving: A simulator study.* Accid Anal Prev, 2012. **45**(2): p. 493-7.
710. Hartman, R.L., et al., *3,4-Methylenedioxymethamphetamine (MDMA) and metabolites disposition in blood and plasma following controlled oral administration.* Anal Bioanal Chem, 2014. **406**(2): p. 587-99.

711. Schwaninger, A.E., et al., *Stereoselective urinary MDMA (ecstasy) and metabolites excretion kinetics following controlled MDMA administration to humans.* Biochem Pharmacol, 2012. **83**(1): p. 131-8.
712. Ludewig, S., et al., *No lasting effects of moderate doses of MDMA (Ecstasy) on memory performance and mood states in health humans.* . Biol Psychiatry, 2003. **52 (Suppl) .** p. 205S.
713. Frei, E., et al., *Localization of MDMA-induced brain activity in healthy volunteers using low resolution brain electromagnetic tomography (LORETA).* Hum Brain Mapp, 2001. **14**(3): p. 152-65.
714. Vollenweider, F.X., et al., *Opposite effects of 3,4-methylenedioxymethamphetamine (MDMA) on sensorimotor gating in rats versus healthy humans.* Psychopharmacology (Berl), 1999. **143**(4): p. 365-72.
715. Chang, L., et al., *Effect of ecstasy [3,4-methylenedioxymethamphetamine (MDMA)] on cerebral blood flow: a co-registered SPECT and MRI study.* Psychiatry Res, 2000. **98**(1): p. 15-28.
716. McNamara, R., M. Maginn, and A. Harkin, *Caffeine induces a profound and persistent tachycardia in response to MDMA ("Ecstasy") administration.* Eur J Pharmacol, 2007. **555**(2-3): p. 194-8.