Progress in Neuro-Psychopharmacology & Biological Psychiatry 64 (2016) 237–249

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

# MDMA-assisted therapy: A new treatment model for social anxiety in autistic adults☆

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ARTICLE INFO

Available online 25 March 2015

*Keywords:*
Autism
Ecstasy
MDMA
Psychedelics
Psychotherapy
Social anxiety

ABSTRACT

The first study of 3,4-methylenedioxymethamphetamine (MDMA)-assisted therapy for the treatment of social anxiety in autistic adults commenced in the spring of 2014. The search for psychotherapeutic options for autistic individuals is imperative considering the lack of effective conventional treatments for mental health diagnoses that are common in this population. Serious Adverse Events (SAEs) involving the administration of MDMA in clinical trials have been rare and non-life threatening. To date, MDMA has been administered to over 1133 individuals for research purposes without the occurrence of unexpected drug-related SAEs that require expedited reporting per FDA regulations. Now that safety parameters for limited use of MDMA in clinical settings have been established, a case can be made to further develop MDMA-assisted therapeutic interventions that could support autistic adults in increasing social adaptability among the typically developing population. As in the case with classic hallucinogens and other psychedelic drugs, MDMA catalyzes shifts toward openness and introspection that do not require ongoing administration to achieve lasting benefits. This infrequent dosing mitigates adverse event frequency and improves the risk/benefit ratio of MDMA, which may provide a significant advantage over medications that require daily dosing. Consequently, clinicians could employ new treatment models for social anxiety or similar types of distress administering MDMA on one to several occasions within the context of a supportive and integrative psychotherapy protocol.



## 1. Introduction

The purpose of this paper is to provide an overview of the rationale and to summarize the method for a pilot study of 3,4-methylenedioxymethamphetamine (MDMA)-assisted therapy for the treatment of social anxiety in autistic adults. Multiple areas of investigation in autism research have paralleled MDMA research. Some examples include neurobiological studies, particularly on the effects of the neuropeptides oxytocin (OT) and vasopressin, which are believed to play a role in interpersonal connection and bonding (Domes et al., 2007a,2007b; Dumont et al., 2009; Hollander et al., 2003, 2007; Jacob et al., 2007; Kirsch et al., 2005; Lerer et al., 2008; Sumnall, 2006), and the neurotransmitter serotonin (Volkmar et al., 2009; Vollenweider et al., 1998; Whitaker-Azmitia, 2005). Cognitive studies, such as investigations of the mechanisms of face recognition, also appear in the literature of both autism (Adolphs et al., 2001; Ashwin et al., 2007, 2009; Clark et al., 2008) and MDMA research (Hoshi et al., 2004).

Functional brain imaging studies with anxiogenic stimuli in autistic individuals suggest that the amygdala may be differentially activated, with greater activation in the anterior cingulate gryus and

*Abbreviations:* $5HT_{1A}$, 5-hydroxytryptamine (serotonin) receptor 1A; 8-OH-DPAT, 7-(Dipropylamino)-5,6,7,8-tetrahydronaphthalen-1-ol; ADOS-2, Autism Diagnostic Observation Schedule, Second Edition (Module 4); BDI, Beck Depression Inventory; CAPS, Clinician-Administered PTSD Scale; C-SSRS, Columbia Suicide Severity Rating Scale; DEA, Drug Enforcement Administration; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th edition; EKG, Electrocardiogram; ERQ, Emotion Regulation Questionnaire; FDA, Food and Drug Administration; IRB, Institutional Review Board; IRI, Interpersonal Reactivity Index; LSAS, Liebowitz Social Anxiety Scale; LSD, Lysergic Acid Diethylamide; MAOI, Monoamine Oxidase Inhibitor; MDMA, 3,4-methylenedioxymethamphetamine; OT, Oxytocin; PSS, Perceived Stress Scale; PTSD, Posttraumatic Stress Disorder; RSES, Rosenberg Self-Esteem Scale; SAE, Serious Adverse Event; SCID-I-RV, Structured Clinical Interview for Diagnoses Axis I Research Version; SSRI, Selective Serotonin Reuptake Inhibitor; STAI, State-Trait Anxiety Index; SUDS, Subjective Units of Distress; TAS-20, Toronto Alexithymia Scale; TASIT, The Awareness of Social Inference Test; TD, Typically Developing; UML, 1-Methyl-D-Lysergic Acid Butanolamide; U.S., United States; VHD, Valvular Heart Disease.

☆ Trial Registration ClinicalTrials.gov Identifier: NCT02008396

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http://dx.doi.org/10.1016/j.pnpbp.2015.03.011

superior temporal cortex, and less activation in the left amygdala and left orbito-frontal cortex (Ashwin et al., 2007), or it may signal in an atypical manner to the fusiform gyrus, a key brain region involved in facial recognition, resulting in differences in social perception between autistic and typically developing (TD) individuals (Hall et al., 2010). In TD healthy volunteers, MDMA administration acutely decreases activity in the left amygdala (Gamma et al., 2000), a brain region involved in the interpretation of negative cues, and attenuates amygdalar response and emotional reactivity to angry faces (Bedi et al., 2009). This action of MDMA is compatible with its reported reduction in fear of emotional injury or defensiveness (Greer and Tolbert, 1986). The multi-level effects of MDMA on brain circuits, monoaminergic neurotransmitters, and neurohormones that have been studied extensively in autistic individuals suggest that further study of the effects of MDMA in autistic populations is warranted. In addition, MDMA has been proposed as a treatment for anxiety disorders (Johansen and Krebs, 2009), which are prevalent in autistic individuals (Gillott and Standen, 2007). The current review takes into account these areas of overlap and explores a parallel indication by studying MDMA-assisted therapy as an intervention for social anxiety in autistic adults.

### 1.1. Relevant history

MDMA, also known as the street drug Ecstasy or Molly, is a psychoactive compound with structural similarities to both amphetamine and the hallucinogenic phenethylamines (Grob and Poland, 1995). MDMA is a laboratory-synthesized compound that does not exist on its own in nature. Even though MDMA has been illegal in the United States since the mid-1980s, there were 0.8 million past-year initiates who reported first-time Ecstasy use in 2013 (Substance Abuse and Mental Health Services Administration, 2014).

MDMA was developed as a byproduct of a styptic compound at Merck in Germany in 1912. University and industry based medicinal chemists started conducting initial scientific investigations during the 1970s after chemist Alexander Shulgin began exploring MDMA's potential to create controllable altered states of consciousness. Despite reported therapeutic potential (Greer and Tolbert, 1986; Grinspoon and Bakalar, 1986), concerns about potential neurotoxicity resulted in suppression of FDA-approved research with human subjects in clinical investigations. Gross errors in reporting on MDMA's effects, side effects, and risk factors in non-human primate studies (e.g., Ricaurte et al., 2003), in addition to problems with interspecies scaling algorithms leading to overdosing by an order of magnitude in animal studies (Baumann et al., 2007), have contributed to confusion about which policies and approaches are optimal regarding regulation and research.

Early investigators noted MDMA's capacity to help people talk openly and honestly about themselves and their relationships, without defensive conditioning intervening (Greer and Tolbert, 1986; Stolaroff, 2004). For several hours, anxiety and fear appeared to decrease, even in subjects who were chronically constricted and apprehensive. Of particular interest to psychiatric researchers were clients with disorders such as chronic post-traumatic stress disorder (PTSD) and depression who were nonresponsive to conventional treatment models. Beginning

**Table 1**
Major studies implicating the effects of MDMA.

| Year | Citation | Sample | Category | Significance |
|---|---|---|---|---|
| 1986 | Greer & Tolbert | 29 | Psychotherapy | First published report |
| 1998 | Grob | 18 | Phase 1 — Preliminary | Controlled study |
| 2008 | Bouso et al. | 6 | Psychotherapy | Controlled study (incomplete) |
| 2011 | Mithoefer et al. | 20 | Psychotherapy | Blinded, placebo controlled RCT |
| 2013 | Mithoefer et al. | 16 (CAPS); 19 (Questionnaire) | Psychotherapy (see above) | Long term follow up of above |
| 2013 | Oehen et al. | 12 | Psychotherapy | 2nd RCT, active placebo |
| 2000 | Gamma et al. | 16 | Mechanism of action | PET study — < L amygdala |
| 2009 | Dumont et al. | 15 | Mechanism of action | Elevated OT in an RCT |
| 2009 | Bedi et al. | 9 | Mechanism of action | fMRI of brain — lower amygdala to angry faces |
| 2014 | Carhart-Harris et al. | 19 | Mechanism of action | Worst memories less distressing & vivid |
| 2014 | Bedi et al. | 13 | Mechanism of action | Increased social language RCT |
| 2014 | Hysek et al. | 32 | Mechanism of action | Increased emotional empathy, prosocial in men |
| 2014 | Kuypers et al. | 20 | Mechanism of action | Plasma OT after MDMA unrelated to empathy |
| 2012 | Hysek et al. | 48 | Mechanism of action | Changes in emotion reading, self-reported increased closeness, elevated OT |
| 1996 | Grob et al. | 6 | Pharmacodynamics/PK | Reported cardiovascular, increased cortisol, prolactin |
| 1998 | Vollenweider et al. | 13 | Pharmacodynamics/PK | Subjective, cardiovascular, neuroendocrine & spont. reactions |
| 2000 | de la Torre et al. | 14 (6 in study 1; 8 in study 2) | Pharmacodynamics/PK | Detected nonlinear pharmacokinetics |
| 2001 | Liechti and Vollenweider | 16 | Pharmacodynamics/PK | Using pretreatment studies, shows impact of 5HT release on MDMA effects |
| 2001 | Liechti et al. | 74 (incl. earlier FXV samples) | Pharmacodynamics/PK | Pooled data — women report greater subjective effects & reactions, men higher cardiovascular |
| 2014 | Kirkpatrick et al. | 220[a] (contains de Wit, ME Liechti data) | Pharmacodynamics/PK | Demonstrates similarity of MDMA effects across 3 independent laboratories |
| 2006 | Mechan et al. | 4 squirrel monkeys | PK/risks and toxicity | Detected nonlinear PK in monkeys, and demonstrates doses deemed "human equivalent" weren't. |
| 2009 | Rogers | Review/meta analysis | PK/risks | Systematic review and meta-analyses of literature concluding Ecstasy use may produce significant but small impairments and can but mostly won't be fatal |
| 2007 | Schilt | 58 Ecstasy users, 60 controls | PK/risks | First prospective study of effects of Ecstasy use. Reported impaired (actually less improvement) in verbal memory but no other areas. |
| 2011 | Halpern | 52 Ecstasy users; 59 controls matched for drug use | PK/Risks | Study strongly controlling for drug use histories and using low drug use sample. Found few differences in cognitive performance save poorer strategic self-regulation in Ecstasy users |
| 2010 | Nutt et al. | 20 substances | Risks/benefits | Modeling determined alcohol, heroin most harmful; [magic] mushrooms, buprenorphine last (i.e. least harmful); MDMA 17/20 on list. |
| 2010 | Van Amsterdam et al. | 19 substances | Risks/benefits | Used similar team and produced similar but not identical rankings. In this model, Ecstasy 14th of 19, rated slightly more harmful than Nutt et al. |
| 2007 | Sessa | Review | Therapy assessment | Argues for use of MDMA in psychotherapy |
| 2009 | Johanson and Krebs | Review | Review | Provides hypotheses and model for how MDMA might help treat anxiety disorders |

[a] The Basel sample is not the same as the Zurich sample so the two sets represent independent data samples. However, Kirkpatrick et al. may cover data addressed in reports by the Basel (Hysek–Liechti) team and at least of the Bedi/De Wit data (when collected at the University of Chicago).

in the mid-1970s, therapists and psychiatrists provided the still-legal MDMA to thousands of clients as an adjunct to therapy, but unfortunately no methodical research was published from this period.

Formal hearings commenced in 1985 to determine MDMA's legal status. Weighing the interests of the therapeutic community against the growing perception of MDMA's abuse liability and the threat it posed to public health and safety, the U.S. Drug Enforcement Administration (DEA) eventually ordered that it be placed in the most restrictive category, Schedule I, in 1986 (Lawn, 1986).

In the decades following the DEA scheduling, discord and divisiveness escalated in the research world. At the center of the debate was the question of whether or not MDMA use caused neurotoxicity resulting in brain damage. Histopathological findings in animal studies with repeated "binge administration" injections demonstrated that distal serotonergic axonal degeneration could result with doses much higher than recreational users consume (Sumnall, 2006). Implications of such pre-clinical findings are further confounded by observations of proximal axonal regeneration, cell body sparing, and absence of standard laboratory markers of neurotoxicity. Some studies suggested that even modest use could lead to irreparable organic and psychiatric damage, which included emotional and memory deficits, although these reports were often marred by flawed research methodologies, questionable data analyses, and biased conclusions (Danforth and Grob, 2009; Grob, 2000, 2005; LeVay, 2008).

The Ecstasy user literature base also contains multiple factors that limit the generalizability of naturalistic studies of street Ecstasy to clinical settings in which pure MDMA is administered from one to several times within a psychotherapy paradigm. The most substantial of these limitations are the high quantities of doses taken in nearly all publications on recreational Ecstasy users, often on the order of several hundreds of doses. Critics of MDMA-assisted psychotherapy use this data to suggest a higher level of risk than logically can be inferred from no more than six exposures reported in MDMA-assisted psychotherapy clinical trials (e.g., Parrott, 2014). Additionally, "Ecstasy" refers to MDMA obtained from street sources which currently is almost always cut with other drugs as seized shipments from 2007 show only 3% of tablets destined for North American markets containing pure MDMA (Hudson et al., 2014) (https://www.ecstasydata.org/stats.php). Authors commonly cite Ecstasy user data and use it to draw conclusions about MDMA without citing the above purity limitation (Grob, 2000). Furthermore, Ecstasy users are also almost always polysubstance abusers as indicated in the 2007 *National Epidemiologic Survey on Alcohol and Related Conditions* (n = 43,093) (Wu et al., 2009), and high polysubstance abuse rates confound nearly all of the Ecstasy correlations found in the medical literature to date. Other common notable hazards include adverse environmental conditions, polydrug use in dangerous combinations, and ingestion of high doses or stacking multiple doses to prolong drug effects. Therefore, research on recreational Ecstasy use has limited applicability to determining the safety of clinical investigations of MDMA-assisted therapy.

### 1.2. Pharmacology and behavioral effects in animals

Research into the pharmacological, physiological, or psychological effects of MDMA began in the 1950s, when the U.S. Army administered MDMA to guinea pigs, monkeys, mice, rats, and dogs as part of a military research program, possibly intended to develop chemical incapacitants or means of enhancing interrogation (Hardman et al., 1973). Investigations of the pharmacology, functional effects, and toxicity of MDMA in animals have generally included injections of large and often repeated doses of MDMA in an attempt to produce human-equivalent doses (Baggott et al, 2001). Recent reports re-examining these effects have questioned the applicability of interspecies scaling models for MDMA, and have supported nonlinear pharmacology (Baumann et al., 2009; Mechan et al., 2006; Wang et al., 2005).

A study directly comparing MDMA pharmacokinetics in humans and monkeys found that the two species metabolized MDMA in a similar but not identical manner and that MDMA had a shorter half-life in monkeys than in humans. Both species exhibited nonlinear pharmacokinetics, and it appears that monkeys and humans exhibit similar plasma MDMA levels after receiving the same dose of MDMA (Mueller et al., 2009a,2009b). An investigation in rats also demonstrated nonlinear pharmacokinetics in that species as well, finding that human-equivalent doses of MDMA in rats are close to or identical to those in humans and drug half-life is rapid (Baumann et al., 2009). Doses of 10 mg/kg, but not 2 mg/kg, produced signs of serotonin syndrome in rats, but neither dose reduced total serotonin levels in the brain two weeks after drug administration. These discoveries suggest that toxicological and behavioral studies of MDMA used doses exceeding human equivalent doses. As a consequence, it is difficult to interpret the relevance of findings in nonclinical studies employing these dosing regimes.

Early studies in rodents suggest that $5HT_{1A}$ receptors reduce anxiety and aggression (Brunner and Hen, 1997; Graeff et al., 1996), and some drug discrimination studies suggest that the $5HT_{1A}$ agonist 8-OH-DPAT partially or fully substitutes for MDMA (Glennon and Young, 2000; Glennon et al., 2007; Schechter, 1986). Administering a $5HT_{1A}$ antagonist attenuates the prosocial behavior of rats, measured by preference to lie adjacent to each other, possibly because it prevents elevation in OT (Morley et al., 2005; Thompson et al., 2007). At least some direct or indirect effects of MDMA on serotonin receptors may cause changes in GABA uptake in the ventral tegmental area of rats (Bankson and Yamamoto, 2004). In rodents, doses of MDMA equivalent to human doses produce either few or no behavioral effects. However, doses of 5 mg/kg or greater have several specific behavioral effects, including increased locomotor activity, increased anxiety at moderately high doses, and decreased anxiety at higher doses (Cole and Sumnall, 2003; Green et al., 2003). In contrast, rhesus monkeys do not exhibit increased locomotor activity after receiving up to 2.4 mg/kg MDMA (Crean et al., 2006).

To date, no empirical investigations have been conducted on the effects of MDMA on primate social interactions. Morley and colleagues observed rat behavior after receiving 5 mg/kg MDMA, noting that this dose correlated with prosocial behavior, such as lying next to each other (Morley et al., 2005). Recent studies conducted by the same team of researchers suggest that MDMA increases prosocial behavior in rats by elevating OT in the paraventricular nucleus through 5HT1A receptor agonism, with the OT increase arising from the indirect effects of MDMA on 5HT1A receptors (Thompson et al., 2007, 2009). At present, 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 (Hasler et al., 2009; Hysek et al., 2010; van Wel et al., 2012). 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 (Liester et al., 1992; Peroutka et al., 1988; Solowij et al., 1992; Vollenweider et al., 1998).

### 1.3. Summary of effects of MDMA in humans

MDMA is primarily a potent releaser of serotonin as well as an inhibitor of presynaptic serotonin, dopamine, and norepinephrine (de la Torre et al., 2004). Pharmacologically it exhibits effects similar to amphetamine type drugs, with a chemical structure that also resembles the classic hallucinogen mescaline. The primary mode of action of MDMA is as an indirect serotonergic agonist, increasing the amount of serotonin released into the synaptic space. MDMA interacts with the serotonin transporter, and is transported into the nerve terminal, facilitating the release of serotonin. After oral ingestion, MDMA is readily absorbed from the gastrointestinal tract.

At doses of at least 1 mg/kg (or approximately 70 mg) and higher, active doses of MDMA alter mood and cognition and produce slight

alterations in perception (Dumont and Verkes, 2006; Liechti et al., 2001). Its onset of action is within 30–45 min of intake, and effects peak 90 to 120 min after oral administration, and they are near to or at pre-drug levels 3 to 6 h later (Lamers et al., 2003; Tancer and Johanson, 2001; Vollenweider, 1998). Sub-acute effects may occur one to three days after drug administration, but are no longer apparent seven to 14 days later (Harris et al., 2002; Huxster et al., 2006; Pirona and Morgan, 2010). The elimination half-life is approximately 7 h. MDMA's primary metabolite, 3-4 methylenedioxyamphetamine (MDA), has a longer half-life of approximately 16–38 h. Primary enzymatic activity responsible for the metabolism of MDMA occurs at the hepatic cytochrome P45 CYP2D6 enzyme. MDMA is metabolized in a non-linear manner with relatively small increases in dose causing disproportionate elevation in MDMA plasma concentration, consequently necessitating vigilance for the development of signs of acute adverse reactions (Harris et al., 2002; Mas et al., 1999).

*1.3.1. Physiological effects*

MDMA acutely increases cortisol, prolactin, and adrenocorticotropic hormone concentrations in a dose-dependent manner (Farré et al., 2004; Grob et al., 1996; Harris et al., 2002; Mas et al., 1999; Parrott et al., 2008). MDMA also produces a robust increase in the neurohormone OT (Dumont et al., 2009). OT is a neuropeptide associated with pair bonding and social affiliation in mammals that also attenuates amygdalar response to anxiogenic stimuli (Adolphs et al., 2005; Bartz and Hollander, 2006). Exogenous OT administration is associated with increased interpersonal trust and changes in social perception, including attenuated reactivity to threatening faces (Domes et al., 2007a, 2007b; Kosfeld et al., 2005). OT administration also improves empathic accuracy in some individuals who are shy or lack adequate social skills (Guastella et al., 2010). Alterations in OT signaling have also been proposed as a potential mechanism for the underlying neurological basis for the core social differences in autism and have been implicated as a possible novel therapy for enhancing social adaptability (Bartz and Hollander, 2006).

MDMA elevates OT in peripheral blood (Dumont et al., 2009; Hysek et al., 2012; Wolff et al., 2006), which is an imperfect but somewhat reliable indicator of elevated OT in the brain (Bartz and Hollander, 2006). Findings of an association between elevated OT and detectable MDMA in peripheral blood were first reported in a naturalistic study of London nightclub attendees with and without detectable plasma MDMA levels (Wolff et al., 2006). Dumont and colleagues reproduced these results in humans and found that MDMA significantly elevated peripheral plasma OT levels in a placebo-controlled study in healthy volunteers (Dumont et al., 2009), in addition to a positive association between elevated levels of OT and prosocial feelings. Hysek and colleagues replicated these results and further reported that administering a serotonin reuptake inhibitor, but not a norepinephrine uptake inhibitor nor several adrenergic antagonists, attenuated the effects of MDMA on OT levels, suggesting a serotonergic mechanism in producing elevated (Hysek et al., 2012). The effects of MDMA on OT could be partially responsible for changes in empathy (Bedi et al, 2010). However, the multi-level effects of MDMA on monoaminergic signaling and OT, combined with a therapeutic setting focused on enhancing functional skills, are more likely to provide the opportunity for a corrective emotional experience greater than OT alone, and could be useful in the treatment of social anxiety in autistic adults.

Hyperthermia has occurred in people using Ecstasy in unsupervised and non-medical conditions (e.g., vigorous dancing in hot, underventilated spaces without adequate access to water), and though rare, it is one of the most frequently reported SAEs occurring in Ecstasy users (Henry and Rella, 2001; Liechti et al., 2005). In rare but sometimes lethal cases, naïve users have consumed too much water without ingesting required amounts of electrolytes, leading to water intoxication (hyponatremia) (Milroy, 2011). Taking MDMA with monoamine oxidase inhibitors (MAOIs) or with certain antiretroviral medications can induce a life-threatening hypertensive crisis (Harrington et al., 1999; Smilkstein et al., 1987).

MDMA produces sympathomimetic effects that include elevation in blood pressure and heart rate. Elevation in blood pressure above 140/110 or higher occurred in approximately 5% of research participants receiving at least 100 mg MDMA in research studies. However, blood pressure returned to normal as drug effects waned (Downing, 1986; Grob, 1998; Grob et al., 1996; Lester et al., 2000; Liechti et al., 2001; Mas et al., 1999; Vollenweider et al., 1998). The elevation of blood pressure and increased heart rate produced by MDMA, like that produced by other sympathomimetic drugs, can lead to additional risks and complications (Hughes et al., 1993; Kaku and Lowenstein, 1990; Perez et al., 1999), such as stroke, cardiac events or other cerebrovascular events, including cerebral venous sinus thrombosis (Rothwell and Grant, 1993) and cerebral hemorrhage (Gledhill et al., 1993; Henry et al., 1992; Manchanda and Connolly, 1993; Selmi et al., 1995). First-time users with congenital heart defects are especially vulnerable to cardiac events (Hall and Henry, 2006). Due to properly conducted medical screening, there have been no such events to date in any clinical trial of MDMA.

Some researchers expressed concern that MDMA activity at $5HT_{2B}$ receptors might be indicative of increasing risk of valvular heart disease (VHD) with repeated use (Setola et al., 2003). Studies in Ecstasy users indicated that only people reporting average lifetime exposure of 900 tablets had cardiac abnormalities indicative of potential VHD (Droogmans et al., 2007), and a case of VHD has occurred in a man reporting approximately 16 years of Ecstasy use (Montastruc et al., 2012). No abnormalities were found in people reporting lifetime exposure of approximately 200 tablets in the same study. Since VHD-associated changes and VHD only occurred after extremely heavy Ecstasy use, they are unlikely to be a risk within the research or therapeutic context.

Hepatotoxicity (liver disease or damage) was reported in approximately 16% of 199 case reports from non-medical, uncontrolled Ecstasy users, making it the third most SAE reported in the literature (Baggott et al., 2001). No cases of liver disease or hepatotoxicity have occurred in a controlled clinical trial with MDMA.

MDMA is not considered physically addictive, but there have been reports of both acute and chronic psychological reactions in vulnerable individuals (Parrott, 2007). Nevertheless, these cases generally have been in the context of frequent polydrug use, Ecstasy or Molly use of dubious quality, adverse environmental settings, and significant underlying psychological vulnerability (Grob, 2005). Even though Ecstasy is considered a drug of abuse, pure MDMA is not considered a drug of dependence on the order of opioids, amphetamines, methamphetamines, and cocaine. This lack of dependence is evidenced by rodents and non-human primates self-administering MDMA at much lower rates than the aforementioned drugs (De La Garza et al., 2007; Schenk, 2009), and even heavy Ecstasy users fail to report the intensive patterns of use seen with other stimulants. Hence, MDMA possesses moderate abuse liability that is greater than that for serotonergic hallucinogens but less than that for stimulants. Nutt et al. (2010) have studied the relative harm of a variety of drugs and have identified MDMA as being among the least dangerous recreational compounds.

*1.3.2. Neuropsychological effects*

Most of the therapeutic effects of MDMA result from changes in affect, cognition and social interaction. Vollenweider et al., (1998) reported that MDMA produced acute "increased responsiveness to emotions, a heightened openness, and a sense of closeness to other people" (p. 247). When combined with psychotherapy that supports one or more of these effects, MDMA permits individuals to confront and consider emotionally intense memories, thoughts or feelings and perhaps through changes in mood and perception increases empathy and compassion for others and one's self (Bouso et al., 2008; Greer and Tolbert, 1986; Mithoefer et al., 2011).

MDMA facilitates states of positive mood as well as transient anxiety (Camí et al., 2000; Harris et al., 2002; Liechti et al., 2001; Tancer & Johanson, 2001). MDMA users report feeling more talkative and friendly after receiving MDMA, and at least one research team informally reported increased feelings of closeness to others (Vollenweider et al., 1998). However, subjects have also reported feeling anxious and undergoing negatively experienced derealization, including increased anxiety related to loss of control and experiences of racing or blocked thoughts (Camí et al., 2000; Liechti et al., 2001; Vollenweider et al., 1998). Subjects receiving active doses of MDMA experienced euphoria, positive mood, vigor and positively experienced derealization, and they also experienced anxiety, tension and dysphoria, as concern over losing control over the self (Camí et al., 2000; Harris et al., 2002; Tancer & Johanson, 2001; Liechti et al., 2001). Available data is unclear regarding whether the increases in positive and negative mood occur simultaneously or occur at different times throughout the duration of MDMA effects; data in reports from two different teams suggest that peaks in negative mood may precede peaks for positive mood (Tancer & Johanson 2001; Liechti and Vollenweider, 2000). Table 1 lists major studies implicating the effects of MDMA.

### 1.4. Clinical advantages of MDMA

As a clinical intervention to increase social adaptability, MDMA provides specific advantages. In supportive settings, a typical oral dose of 75–125 mg produces psychological effects that are distinct from those of classic hallucinogens (Nichols, 1986; Vollenweider et al., 1998). Beginning in the late 1970s, proponents saw the benefits of MDMA, compared to classic hallucinogens, making it uniquely suited as an adjunct to therapy. It was comparatively mild, shorter acting, and induced an enhanced ability to facilitate heightened states of introspection, all without distracting cognitive distortions and alterations in perception, body image, and sense of self commonly seen with classic hallucinogens, such as LSD, psilocybin, and mescaline. Users were reported as losing defensive anxiety and feeling more emotionally open thus giving them access to feelings and thoughts not ordinarily available to them.

In informal settings, MDMA was reported to be useful in treating a wide range of conditions, including post-traumatic stress, phobias, psychosomatic disorders, depression, suicidality, drug addiction, relationship difficulties and the psychological distress of terminal illness (Adamson and Metzner, 1988; Downing, 1986; Greer and Tolbert, 1986; Grinspoon and Bakalar, 1986; Riedlinger and Riedlinger, 1994). Lasting improvement was often reported in patients' self-esteem, ability to communicate with significant others, capacity for achieving empathic rapport, interest in and capacity for insight, strengthened capacity for trust and intimacy, and enhanced therapeutic alliance (Grinspoon and Bakalar, 1986).

## 2. Phase 1 and Phase 2 clinical studies with MDMA

### 2.1. Establishing safety and feasibility

Recent research with human subjects has focused on establishing safety parameters for limited use of MDMA-assisted therapy in U.S. and European clinical settings (e.g., Mithoefer et al., 2011, 2013; Oehen et al., 2013). The first double-blind, placebo controlled U.S. Phase 1, FDA-compliant study was conducted in 1994, with findings that suggested MDMA may cause a statistically significant increase in body temperature, heart rate, and blood pressure in some healthy volunteers (Grob, 1998; Grob et al., 1996; Lieb et al., 2002). However, these increases were found to be transient and generally tolerable in a controlled clinical setting. Subsequent trials confirmed that MDMA produced significant increases in heart rate and blood pressure that were likely to be well tolerated by healthy individuals (Check, 2004; Doblin, 2002; Hysek et al., 2012; Lieb et al., 2002; von Sydow et al., 2002). As of November 2014, MDMA had been administered to more than 1133 research subjects, in both Phase 1 and Phase 2 studies. Only one expected SAE that was probably drug-related has been reported, which was an increase in frequency of premature ventricular contractions experienced during treatment, which resolved with full recovery to baseline after the effects of MDMA ceased. No acute cardiac damage occurred, and hospitalization during this SAE was a cautionary measure. No unexpected, life-threatening SAEs have occurred in published or ongoing research studies (Jerome and Baggott, 2003; Multidisciplinary Association for Psychedelic Studies, 2015)

### 2.2. MDMA-assisted therapy for PTSD

The first placebo-controlled Phase 2 pilot study of MDMA-assisted psychotherapy for the treatment of chronic, treatment resistant PTSD demonstrated promising results in a sample of 20 subjects (Mithoefer et al., 2011). Scores on the Clinician-Administered PTSD Scale (CAPS), an established gold-standard measure of PTSD symptoms, declined to a statistically and clinically significant degree after undergoing MDMA-assisted psychotherapy. The group of subjects randomized to receive MDMA showed a mean CAPS score reduction of 53.7, with a mean starting score of 79.2, whereas, participants in the placebo arm who also received psychotherapy had a mean starting score of 79.6 and showed a mean CAPS score reduction of 20.5. As a point of comparison, a reduction of mean CAPS scores of 10.2 in a clinical trial of 187 patients resulted in FDA-approval of sertraline (Zoloft) for PTSD (Brady et al., 2000). Improvements in PTSD symptoms observed in the proof of principle study were maintained an average of 3.8 years later ($N = 16$) (Mithoefer et al., 2013). Mithoefer et al., (2011) reported that, "MDMA-assisted psychotherapy with close follow-up monitoring and support can be used with acceptable and short-lived side effects in a carefully screened group of subjects with chronic, treatment-resistant PTSD" (p. 449). A double blind pilot study of MDMA-assisted psychotherapy conducted by a Swiss therapist team in an equivalent Swiss clinical population ($N = 12$) comparing 125 mg MDMA to 25 mg MDMA as an active placebo found a clinically but not statistically significant effect, although trends toward symptomatic improvement were noted using a German translation of the CAPS (Oehen et al., 2013). The improvement continued to increase during the twelve-month follow-up.

Currently, four Phase 2 pilot studies of MDMA-assisted psychotherapy are underway for treatment of chronic PTSD (NCT01689740, NCT01793610, NCT01211405, NCT01958593), including one in traumatized war veterans and as well as first responders, such as police officers and fire fighters. These studies have shown promise for MDMA-assisted psychotherapy to help people overcome PTSD, an anxiety-related disorder, and suggest that this treatment could also be useful in treating social anxiety in autistic adults.

## 3. The need for innovative mental healthcare options for autistic adults

A major revision of autism diagnostic criteria in the in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (American Psychiatric Association, 2013) eliminated the distinctions between autism categories and combined them under one diagnosis. The revised DSM-5 definition includes the former diagnoses of Asperger's Disorder and Pervasive Developmental Disorder. The term *autism* refers to a spectrum of congenital and pervasive neurocognitive variants, characterized, in part, by atypical development of social and communication skills.

At present, there are no published research data in support of any compound that can influence the course of autism or be a causative agent. Autistic adults often present for treatment of conditions such as anxiety, trauma, depression, and social adaptability challenges. However, responses to conventional prescription medications evaluated in TD individuals are often ineffective in autistic individuals (e.g., King et al.,

2009), and mutual difficulties establishing therapeutic rapport between clinicians and clients can interfere with conventional, psychodynamic psychotherapy (Koenig and Levine, 2011; Ramsay et al., 2005). The search for new supportive treatments is relevant given the lack of established or effective treatment options for anxiety, depression, trauma, and other psychological distress in autistic adults.

### 3.1. Pharmacotherapy: few effective options

Clinical diagnoses such as anxiety disorders, depression, obsessive–compulsive disorder, Tourette's syndrome, tics, and epilepsy are common in autistic populations (Barnhill and Myles, 2001; Canitano and Vivanti, 2007; Cath et al., 2008; Duggal et al., 2001; Frazier et al., 2002; Newman and Ghaziuddin, 2008; Saulnier and Volkmar, 2007; Tsai, 2006; Wymbs et al., 2005). Conventional anti-anxiety medications, including selective serotonin reuptake inhibitors (SSRIs), MAOIs, and benzodiazepines, lack substantial clinical effectiveness in autistic adults, potentially due to physiological differences between autistic and TD individuals. There may be underlying biological reasons for this difference, including some reported evidence for a lower number of benzodiazepine binding sites in the brains of autistic adults (King et al., 2009; Oblak et al., 2012).

Medications approved for the treatment of other indications are often prescribed "off-label" without the Food and Drug Administration (FDA) approval for the use in autistic children, adolescents, and adults. For example, off-label prescription of SSRIs is on the rise in this population (Hollander et al., 2012). The data on SSRIs in the treatment of autistic individuals are of varied nature. Given the paucity of confirmed efficacy in clinical trials and clinical practice, the search for effective, complementary and alternative interventions for mental health issues in autistic populations remains urgent.

### 3.2. Social anxiety and autism

Social anxiety, also known as social phobia, is characterized by fear of scrutiny and avoidance of social interactions (American Psychiatric Association, 2013). Social anxiety is prevalent (Kessler et al., 1994), begins early (Hazen and Stein, 1995; Öst, 1987), and follows a chronic course (Reich et al., 1994). Impairment is substantial in TD individuals (Schneier et al., 1994), and fear and avoidance behaviors interfere with ability to work, attend school, and develop relationships, leading to low quality of life (Liebowitz et al., 1985; Turner et al., 1986).

Comparative studies suggest that autistic adults, especially those who can speak and whose autism might not be immediately recognizable to others and who are faced with strong pressure to conform to non-autistic social norms, are at greater risk for lifetime and current psychological disorders, especially social anxiety (Joshi et al., 2012; Tantam, 1991, 2000). Social anxiety frequently compounds the considerable social challenges experienced by autistic adults (White et al., 2010).

## 4. Factors in support of MDMA-assisted therapy for social anxiety in autistic adults

The primary purpose of this paper is to provide an overview of three main factors that supported the rationale for commencing the first pilot study of an MDMA-assisted therapy treatment model for an adult autistic population. The first factor is clinical findings in reports from early research with psychedelics in studies with autistic minors. The second factor is improved methodology for conducting safe and ethical research with psychedelics and MDMA, especially in vulnerable populations. The third, and most recently available, factor in support of commencing a pilot study is copious anecdotal support culled from public sources and scholarly exploratory inquiry.

### 4.1. Early psychedelics research with autistic minors

Psychedelics are a large class of natural and synthetic substances with limited abuse liability and psychoactive properties that alter thought, mood, and perception in characteristic ways that can resemble dreaming, psychoses, and ecstatic religious experiences. The term is often used synonymously with hallucinogens in the medical literature. However, with psychedelics, the perceiver retains awareness of the illusory and personal nature of the altered perceptions (Aleman and de Haan, 1998). MDMA is difficult to classify because it causes fewer and attenuated hallucinogenic effects (Nichols, 1986) with less cognitive distortion (Grinspoon and Bakalar, 1986) than other classes of psychedelics. MDMA also has mild to moderate amphetamine-like effects and produces subjective prosocial effects which are distinct from the mysticospiritual effects of the classic hallucinogens. Whereas MDMA and classic hallucinogens have different neurobiological mechanisms of action, they share similar psychological effects of catalyzing states of openness and introspection. Therefore, a review of prior research with classic hallucinogens with autistic minors is relevant to a discussion of MDMA-assisted therapy for autistic adults with social anxiety.

From the late 1950s to the early 1970s, researchers in the United States, Europe and Argentina (e.g., Abramson, 1960; Bender et al., 1962, 1963; Fisher and Castile, 1963; Freedman et al., 1961; Simmons et al., 1972, 1966) experimented with therapeutic applications of synthetic psychedelic compounds, mainly LSD, UML (a methylated derivative of LSD), and psilocybin, in attempts to "treat" autistic children during an era when autism was mistakenly considered a form of juvenile schizophrenia until clinical interest declined when funding for research and access to psychedelics decreased due to illicit use and political pressure (Sigafoos et al., 2007). Whereas giving powerful psychedelics to distressed, non-speaking children seems inappropriate according to current ethics and safety standards, in the 1950s and 1960s, synthetic psychedelics were considered new and novel medications with a favorable safety profile that held promise for treating, what were considered at the time, autistic-type developmental disorders in youth.

Researchers shared the common goal of breaking through what they interpreted as the "autistic barrier" toward increased empathic affect and attachment in the absence of effective interventions for behaviors such as self-harm (Mogar and Aldrich, 1969). However, the rationales for conducting the research varied. Some studies emphasized a medical approach. For example, the prospect of restoring speech as a means to reduce isolation inspired some investigators after case reports were published on catatonic schizophrenic adults who were electively mute at baseline but who spoke while under the effects of LSD (Cholden et al., 1955; Freedman et al., 1961). Employing a neurobiological approach, Bender et al., (1963) made early attempts to understand the role of the neurotransmitter serotonin by including biochemical tests in LSD study protocols.

Other researchers emphasized subjective considerations. Fisher (1970), for example, took a psychodynamic approach when providing LSD and psilocybin to autistic children. Fisher emphasized the potential of psychedelics to augment the psychotherapeutic alliance: "Little of what may be called health or growth can occur without legitimate and honest relationships between people. The drugs were, however, in our judgment, of extreme importance in making the psychotherapeutic experience" (p. 112).

From 1959 to 1970, more than 100 minors with the obsolete diagnosis of juvenile schizophrenia, autistic type or similar descriptions were given psychedelics in approximately a dozen trials of varying sizes and durations. In at least six studies, children as young as five years old were given repeated moderate to high doses (100–300 μg) of LSD (e.g., Abramson, 1960; Fisher, 1970; Simmons et al., 1972). In retrospect, the methods employed were flawed to varying degrees according to current standards, including: small sample size (e.g., Rojas-Bermúdez, 1960; Rolo et al., 1965; Simmons et al., 1966), vague and subjective assessment

of positive and negative drug effects (e.g., Bender et al., 1962, 1963; Freedman et al., 1961; Rolo et al., 1965), absent or incomplete baseline data (e.g., Bender et al., 1963; Rojas-Bermúdez, 1960), and inadequate follow-up data collection (Mogar and Aldrich, 1969). A majority of the early researchers were primarily concerned with observing drug effects and proceeded without a clearly stated treatment hypothesis or random assignment to control groups, and reports on the persistence of post-session effects were vague and inconsistent.

Mogar and Aldrich (1969) published a comprehensive review of seven independent studies of LSD for treatment of emotional distress and social isolation in 91 autistic children (Abramson, 1960; Bender et al., 1962, 1963; Fisher and Castile, 1963; Freedman et al., 1961; Rolo et al., 1965; Simmons et al., 1966). Despite "gross shortcomings" (Mogar and Aldrich, 1969, p. 5) and inconsistencies across the seven studies, the reviewers concluded that there was general consensus among the research teams that the LSD treatment sessions were "effective in characteristic ways," (p. 1) including increased vocabulary, increased emotional responsiveness to others, an elevation in positive mood, and decreases in compulsive behavior (p. 13). Social behaviors, such as eye-to-face contact and engaging with the researchers, were observed more frequently during LSD sessions than in placebo or control sessions. No researchers reported serious side effects, toxicity, or permanent regression following treatment with psychedelics.

The general consensus resulting from the early research was that psychedelics were unlikely to restore speech in non-speaking autistic children. However, most researchers concluded that psychedelics allowed subjects a greater degree of contact with others, regardless of demographics, dose, schedule, or setting (Mogar and Aldrich, 1969). Nevertheless, the Controlled Substances Act of 1970 resulted in an abrupt cessation of virtually all clinical research with psychedelic compounds.

The diagnostic distinctions for less readily apparent manifestations of autism have emerged over the past several decades (Volkmar et al., 1994; Wing, 1981) but were not recognized in the research literature until well after clinical research with psychedelics had ended. Now that research with psychedelic-assisted therapy to promote social adaptability is resuming, investigators can recruit autistic adults who speak or who use text-to-speech technology instead of working with non-speaking children. In the early studies, investigators could not collect self-reported baseline or follow-up data, conduct interviews, confirm informed assent, or communicate verbally with subjects during most experimental psychedelic treatment sessions.

### 4.2. Improved methods and standards for psychedelic research

Few, if any, of the clinical studies conducted with psychedelics between the 1950s and early 1970s would satisfy current design, safety, and ethics requirements for research with human subjects. Among numerous serious shortcomings, most early psychedelic trials lacked rigorous oversight by institutional review boards, adequate data and safety monitoring, or adherence to current best practices for scientific research (e.g., adequate informed consent, random assignment to placebo control groups, double-blinded dosing regimens). Due to restrictions on research using psychedelics with human subjects and the flawed methodology of earlier trials, researchers have had few resources to consult regarding the best methods for optimizing safety during challenging psychedelic experiences. However, guidelines and suggestions for improvements in clinical studies and psychotherapy with psychedelics have been published by reputable investigators and are available to inform new research (e.g., Greer and Tolbert, 1998; Johnson et al., 2008; Richards et al., 1972; Strassman, 1995; Winkelman & Roberts, 2007).

A significant innovation in support of resuming clinical research with psychedelics is the evolved understanding of the importance of set and setting. In psychedelic therapy, set refers to the traits, mind state, and expectations of the subject regarding the session (Strassman, 1995). Grof (1980) also considered the psychotherapist's perception of the nature of the experience, the preparation and pre-session psychotherapy, and the specific technique of guidance employed during the drug experience as contributing to set. *Setting* refers primarily to the external factors that influence the ambiance of the experience for the client. For an ideal setting, Grof (1980) recommended a safe and pleasant environment plus reassuring and nurturing interpersonal support.

### 4.3. First-person reports of MDMA/Ecstasy use by autistic adults

The introduction of the Internet has provided new and effective means for autistic individuals to communicate with others who are both autistic and non-autistic, often with greater ease than in face-to-face situations (Davidson, 2008). Ample anecdotal data regarding the MDMA/Ecstasy experiences of autistic individuals available through spontaneous, first-person accounts posted in online discussion forums provided foundational support for clinical research on MDMA-assisted therapy for social anxiety with autistic adults.

Unsolicited accounts of personal MDMA/Ecstasy use have provided consistent statements about its effects on social behavior. Some comments have included descriptions of overall improvement in functioning, whereas other examples have described psychosocial healing and relief from symptoms such as anxiety and trauma. Another common theme reported is improved connectedness to others. Over 250 accounts that were posted in online discussion forums between 2006 and 2011 (e.g., http://wrongplanet.net, http://www.Erowid.org, http://www.psychforums.com, http://www.bluelight.ru) were reviewed prior to commencing original data collection for exploratory doctoral research on the qualitative MDMA/Ecstasy experiences of autistic adults (Danforth, 2013).

The majority of the testimonials included descriptions of positive outcomes. However, robust dialog about potential drawbacks of improper use also has occurred in online forums. The overall impression presented was that MDMA/Ecstasy can be helpful for some autistic individuals, attention to appropriate set and setting is crucial for positive outcomes, and, as with other interventions, MDMA-assisted therapy might be contraindicated for individuals at risk for potential abuse or adverse outcomes (e.g., individuals with history of addiction or who do not have access to sufficient post-session support). As a caveat, the authors would advise any individual against taking Ecstasy or Molly, which are manufactured and marketed on the illicit market and are subject to rampant drug substitution and often low-quality MDMA.

The dissertation was published as a mixed-methods study to explore how autistic adults experience the subjective effects of MDMA/Ecstasy (Danforth, 2013). The purpose of the qualitative component was to document a comprehensive analysis of emergent themes from interviews and to identify themes of clinical relevance. In addition, subjects from 13 countries submitted quantitative survey data, including 100 MDMA/Ecstasy-experienced individuals (76% males; 24% females) and a 50-subject MDMA/Ecstasy-naïve comparison group (54% males; 46% females). Respondents' ages ranged from 21 to 74 years. The majority of respondents reported accounts of sustained benefits after MDMA/Ecstasy experiences, including improvement of conditions such as trauma and social anxiety that are common in autistic populations.

Two notable findings from survey questions about drug effects were that 91% of respondents reported that they experienced "Increased Feelings of Empathy/Connectedness," and 86% indicated "Ease of Communication" as an effect of their MDMA/Ecstasy use. Positive effects (e.g., joy, openness, enjoying being touched) were reported as more strongly experienced than negative effects, and no subjects rated anxiety symptoms in the "strongly experienced" category. A finding particularly relevant to treating social anxiety was that 72% of MDMA/Ecstasy-experienced participants reported "more comfort in social settings," and 12% indicated that the effect lasted for two or more years. Another positive outcome reported was that 78% of the MDMA/Ecstasy-

experienced group reported "feeling at ease in my own body" as an effect, and 15% indicated that the effect lasted two years or longer.

A finding that might have particular relevance to establishing rapport with therapists in clinical settings was that 77% of the MDMA/Ecstasy-experienced group reported that they found it "easier than usual to talk to others" as an effect of taking MDMA/Ecstasy, and 18% indicated that the effect lasted up to one year or longer. A final finding about the duration of effects that could have implications for psychotherapy for autistic adults was that 22% of the MDMA/Ecstasy-experienced group reported "increased insight into own thought processes" that persisted for two or more years. Despite the researcher's multifold efforts to encourage subjects to disclose negative outcomes and to provide balanced accounts of their experiences, there were no reported moderate or serious, long-term adverse outcomes in the final data set.

## 5. Method

For the present FDA-compliant, IRB-approved pilot investigation of the effects of MDMA-assisted therapy on social anxiety in autistic adults, a placebo-controlled, double-blind methodology is being employed, utilizing an MDMA dosage in the range of 75 mg–125 mg. Twelve subjects will be screened and enrolled into the study and randomized into two groups, with one group of eight subjects receiving the experimental drug (MDMA) and the control group of four subjects receiving an inactive placebo. Both the subject, the clinical treatment team, and Independent Rater assessing treatment outcomes are blind to the condition of treatment. All subjects will receive two separate treatment sessions, spaced approximately one month apart. Participants who receive placebo in the first treatment phase can return for one or two optional open-label treatment sessions with MDMA after the blind is broken after six months of follow-up data collection (Fig. 1).

Subjects receiving MDMA will be divided into two sub-groups, the first group of four subjects receiving 75 mg MDMA at the first session and 100 mg MDMA at the second session. The second sub-group of four subjects will receive 100 mg MDMA at the first session and 125 mg at the second session. The researchers opted for a dose-finding regimen due to anecdotal data that suggested that types of sensory hypersensitivity and emotion regulation challenges common with autism might indicate a lower optimal dosing range for this population. Subjects randomized into the placebo condition will receive inactive placebo at each of the two treatment sessions, but otherwise will participate in the identically structured treatment model and assessment battery as those receiving the active drug.

### 5.1. Screening, eligibility, and preparation

After signing an informed consent, prospective subjects will be screened into the study based on eligibility established on a number of diagnostic instruments, including the Structured Clinical Interview for Diagnoses Axis I Research Version (SCID-I-RV) (First et al., 2012), the Leibowitz Social Anxiety Scale (LSAS) (Liebowitz et al., 1985) and the Autism Diagnostic Observation Schedule (ADOS-2) (Bastiaansen et al., 2011). All subjects must be 21 years or older, have at least two years of college education or the equivalent, have an autism diagnosis confirmed by an Independent Rater who is certified based on research reliability, have moderate to severe symptoms of social anxiety, and be able to safely discontinue any psychotropic medications they are currently being prescribed. They must also have healthy cardiovascular function, as per electrocardiogram and medical history, and not suffer from diabetes, glaucoma, seizures, hypertension, liver disease, glaucoma or any other condition that the investigator or medical monitor believes might interfere with subject participation and safety in the study. Subjects must also be MDMA-naïve and without active substance use disorders. Psychiatric exclusion criteria include family history in first-degree relatives of schizophrenia or bipolar I disorder, or subject diagnoses of active or past psychotic disorder, borderline personality disorder, dissociative identity disorder, eating disorder or active suicidal ideation.

Prior to entry into the study, all subjects will have a physical examination, EKG and baseline labs drawn for measurement of plasma OT, vasopressin and cortisol. Baseline performance using The Awareness of Social Inference Test (TASIT) (McDonald et al., 2006), Emotion Regulation Questionnaire (ERQ) (Gross and John, 2003), Beck Depression Inventory (BDI) (Beck et al., 1996), Perceived Stress Scale (PSS) (Cohen et al., 1983), Interpersonal Reactivity Index (IRI) (Davis, 1980, 1983), Rosenberg Self-Esteem Scale (RSES) (Rosenberg, 1965), and State-Trait Anxiety Index (STAI) (Spielberger et al., 1970) will be examined. The LSAS will be the primary outcome measure.

Prior to the first treatment session, all subjects will receive several preparatory psychotherapy sessions, where the structure of treatment and range of possible effects will be discussed, as will any past or current salient issues in the subject's life. These preparatory sessions will also focus on establishing effective rapport between the subject and the treatment team. Conventional psychodynamic psychotherapy will be employed only on a limited basis, as this type of approach is not indicated in general in autistic populations due to mutual interpersonal barriers to the psychotherapeutic alliance with non-autistic therapists (e.g., Koenig & Levine, 2011; Ramsay et al., 2005). As an alternative, research findings support mindfulness training in autistic populations. In Bögels et al., (2008), autistic children and their parents reported

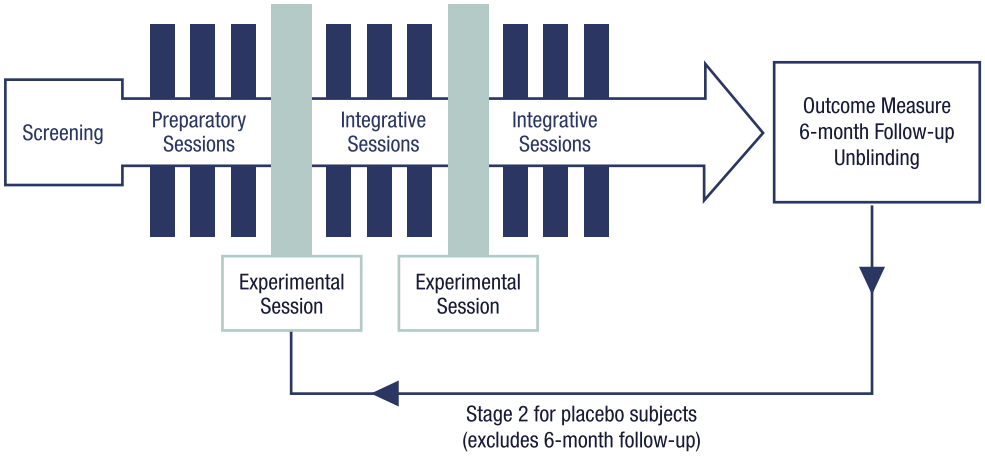


**Fig. 1.** Study structure overview.

improvement in attunement to others, happiness, attention problems, personal goals, self-control, and other measures that contribute to quality of life after receiving mindfulness training. Consequently, all subjects will receive core mindfulness skills training as part of their therapy (Linehan, 1993). An anticipated advantage of this intervention is that it will provide vocabulary, concepts, and skills that support research subjects with transitioning into MDMA-influenced cognitive and affective states as well as communicating with others during a novel, often ineffable, altered state of consciousness.

### 5.2. Treatment sessions

On the days of the two treatment sessions, subjects will arrive at the clinical research center early in the morning, accompanied by a study partner, who has previously committed to driving the subject to and from research sessions, as well as to and from day-after integrative sessions. Office visits as well as treatment sessions will take place in a specially prepared room, which has been designed to minimize sensory distress (e.g., soft lighting, comfortable seating, minimal noise) and to resemble a comfortable den-like space more than a clinical setting. Water intake will be monitored to avoid dehydration or water intoxication, and optional snacks and a light meal will be made available two hours after the study drug is administered. The treatment sessions will be videotaped, though contingent upon subject consent. Prior to experimental drug administration on treatment session days, subjects will have baseline blood pressure, heart rate and temperature measured, with hourly repeat measurements following administration of active drug or placebo for the next seven hours until the conclusion of the treatment session. Suicidal ideation with the Columbia Suicide Severity Rating Scale (Posner et al., 2011) and subjective units of distress (SUDs) will also be assessed during hourly intervals. During the second experimental treatment session, in the late morning, blood will be drawn for later analyses of OT, vasopressin and cortisol. During the actual drug-assisted treatment sessions, both structured and unstructured tasks will be employed, including but not limited to listening to preselected music, working with art supplies, writing in journals, silent introspection, and engaging in rapport building interactions with therapists. In addition, subjects will complete the TASIT, which is an interactive, video-based assessment of social inference skills. The co-therapists, always one male and one female to manage potential transference during therapy, will emphasize creating and communicating a setting of safety and support for the subject during periods of inner focus. More structured interaction during experimental sessions will focus on challenges subjects have had with social perception and function.

### 5.3. Post-session follow-up

The day following each of the two experimental treatment sessions, subjects will return to the study location for an integrative session, where safety data will be collected, the content of the previous day's experience will be examined and methods for adjusting back to daily life after treatment will be reviewed. Additional in-person integrative psychotherapy sessions will be scheduled at two week intervals for one month and then again at the six-month follow-up point. Telephone safety checks will occur daily for the week following treatment sessions, overlapping with the 3–4 days for the drug to be excreted from the body. One day, two weeks and four weeks post experimental drug treatment subjects will complete the BDI, STAI, and PSS. At monthly intervals, between the one-month post-treatment integrative psychotherapy session and the six-month in-person final integrative psychotherapy session, subjects will complete the BDI, STAI, and PSS via remote, secure internet connection. In addition to baseline measures, the LSAS will be conducted the day after experimental treatment sessions, at two-week intervals for one month and then at the six-month follow-up. TASITs will be conducted at baseline, the day of the two experimental treatment sessions, two weeks following each of the treatments and at the six-month follow-up. A subsequent data analysis will evaluate outcomes of active drug versus placebo. Additionally, two post-treatment late-morning blood draws for plasma OT, vasopressin and cortisol will be conducted one month and six months after experimental treatment.

## 6. Concluding remarks

Promising findings from early psychedelics studies with autistic minors, development of safer clinical research models and methods, clarification around optimal set and setting, and an abundance of self-reported accounts of potential benefits all support the case for initiating a pilot trial with MDMA-assisted therapy for autistic adults who have moderate to severe social anxiety.

Researchers gradually and cautiously are exploring a broader range of potential risks and benefits of MDMA-assisted therapies. In the opinion of the authors, this is the optimal and responsible option for addressing the public health concerns that have been raised, as well as to investigate the potential of developing new and novel models for some psychiatric conditions that are refractory to conventional treatment. Informed understanding of the facts about MDMA, a psychotherapeutic compound known to enhance prosocial behaviors, is as relevant to clinicians, researchers, the public, and policymakers now as in any earlier point in its history.

## Acknowledgments

Sponsor funding support provided by the Multidisciplinary Association for Psychedelic Studies (MAPS), a 501(c)(3) non-profit research and educational organization. Berra Yazar-Klosinski, Ph.D. is employed by the sponsor as the Clinical Research Scientist and monitors the study. Additional private funding provided through a donation from the Betsy Gordon Foundation. Nick Walker, M.A. provided consultant services in support of using appropriate and unharmful language to discuss autism in a psychiatric context.

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