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## MDMA-Assisted Psychotherapy for Posttraumatic Stress Disorder

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# Contents

*Fear is the mind-killer.*

- *Frank Herbert, Dune*

# MDMA-assisted psychotherapy for Posttraumatic Stress Disorder

## 1. Introduction

Psychedelic substances have been used for proto-therapeutic purposes for thousands of years (Winkelman & Roberts, 2007). After the discovery of LSD (lysergic acid diethylamide) in 1943 (Hofmann, 2013), western medicine took note of psychedelic substances as possible psychiatric medications – or psychotherapeutic adjuncts respectively – and began exploring their potential. By 1965, over 2,000 papers had been published. However, at that time research was lacking basic theoretical concepts and was largely following a crude methodology (Sessa, 2005). The impact of psychedelic substances in the medical field was soon surpassed by their ill-fated impact in western popular culture during the 1960s (Hofmann, 2013). In the following, the prohibition of those substances effectively halted clinical research before their actual medical potentials could be investigated systematically and thoroughly. For the next decades, the topic was either met with ignorance or contempt in the field of mental health. The predominant view on psychedelic substances was pathological; their medical potential seemed forgotten.

It was not until the end of the twentieth century that systematic clinical research on the mode of action and phenomenology of psychedelic substances was commenced (Gamma, Buck, Berthold, Hell, & Vollenweider, 2000; Strassman, 1995; Vollenweider, Gamma, Liechti, & Huber, 1998; Vollenweider et al., 1997; Vollenweider, Vollenweider-Scherpenhuyzen, Bäbler, Vogel, & Hell, 1998) and not until the mid-2000s that the first randomized controlled clinical trial specifically designed to explore the salutogenetic potential of psychedelic substances was realized (Griffiths, Richards, McCann, & Jesse, 2006).[1] During the following years, further trials were conducted and evidence for the safety, tolerability, and potential therapeutic efficacy of those substances in clinical settings was gathered. Subsequently, the

[1] In this study at the Johns Hopkins University School of Medicine, 72% of the participants ranked their experience occasioned by the classic psychedelic psilocybin among the five most meaningful experiences of their lives. Follow-up studies ascertained the positive effects of these experiences (Griffiths et al., 2011; Griffiths, Richards, Johnson, McCann, & Jesse, 2008; MacLean, Johnson, & Griffiths, 2011).

topic lost much of its overly controversial reputation and chilling effect on academic careers. Eventually, the notable surge in academic interest resulted in therapeutic trials (cf. Bogenschutz et al., 2015; Gasser et al., 2014; Grob et al., 2011; Mithoefer, Wagner, Mithoefer, Jerome, & Doblin, 2011) as well as the usage of psychedelic substances as tools in basic research (cf. Carhart-Harris, Leech, et al., 2014).

In this thesis, the term "psychotherapy with psychoactive substances" is used to describe psychotherapeutic methods that apply psychoactive substances as tools to assist and intensify a therapeutic process. Respective substances include classic psychedelics, such as LSD and psilocybin, as well as empathogens, such as 3,4-methylenedioxy-*N*-methylamphetamine (MDMA).

Today two factors help facilitate the renewed emergence of the field of psychotherapy with psychoactive substances:

1. The ideologically led and indiscriminate 'war on drugs' that was also imposed on psychedelic substances, is increasingly recognized as a failure by growing parts of the public discourse and academia alike. The issue of psychoactive substances, namely their respective risks and potentials, is finally becoming subject to scientific inquiry, long-held dogmas are being deconstructed (Nutt, 2014). In the case of psychedelic substances, it is becoming clear that their public health risks have been greatly exaggerated[2] and mainstream psychiatry is (re-)familiarizing with their therapeutic potential (Pollan, 2015; Sessa, 2015).
2. Apart from the changing cultural framework, basic knowledge about the psychopharmacological and psychological effects of those substances has reached a point, where research does no longer have to depend on unstructured trial-and-error methods to explore a perceived 'broad potential'. On the contrary: today it is possible to fit psychopharmacological action, models of mental disorders, and psychotherapeutic mechanisms towards tailored treatment protocols for various indications.

[2] In fact, population based studies show that use of psychedelic substances is associated with *reduced* psychological distress (Hendricks, Thorne, Clark, Coombs, & Johnson, 2015; Johansen & Krebs, 2015).

The overarching goal of this thesis is to de-mystify, to de-ideologize this underresearched topic to make it accessible to a mature academic discourse in the first place. The broad topic of therapy with psychoactive substances will be elucidated by the example of MDMA in the treatment of posttraumatic stress disorder (PTSD). It will be an interdisciplinary endeavor, drawing on the fields of psychology and medicine as well as social science. The predominant method will be to collect and connect existing but scattered evidence and explore ways to introduce this seemingly unusual paradigm to clinical psychology, psychiatry and psychotherapy.

Today the majority of the medical-psychotherapeutic discourse focuses on evidence from randomized controlled trials. For practical reasons, this thesis largely stays within the limitations of this methodological approach. It must be explicitly stated that the topic suggests further research applying other – critical and/or qualitative – methodologies.

*Why MDMA?*

Picking MDMA as a substance of interest has a few advantages:

- In fact, the initial reception of MDMA was that of an adjunct for psychotherapy – then it became extremely popular as a recreational drug. While the latter development interrupted research on the original application for over 20 years, the popularity of MDMA as the street drug “ecstasy” made it an exceptionally well researched psychoactive substance.
- MDMA has some psychedelic properties but its effects are not as unusual as those of classic psychedelic substances. As a consequence, the connection to established theories and methods appears to be relatively easy.
- The effects profile of MDMA seems to be well-suited for the treatment of a disorder that is both prevalent and often hard to treat with established methods: PTSD.

This thesis will elaborate those points in detail. To understand the relationship of MDMA-assisted psychotherapy with contemporary mental health services, information on the historical, cultural, and social background of the drug will be provided. In the following, the connectivity of the effects profile of MDMA with contemporary theories on and treatment

options of PTSD will be explored. A main concern is to outline basic principles and effect-factors in the application of MDMA as an adjunct for the psychotherapy of PTSD in practice – this includes the thorough investigation of potential risks and dangers. The status quo of therapeutic research as well as a prospective view on possible developments will be presented.

Naturally, psychotherapy with psychoactive substances cannot be seen apart from cultural, social, and ethical implications and concerns that need to be discussed. Apart from those issues, the paradigm does not only face methodical and theoretical challenges itself, in some regards it also challenges established basic convictions and methods. In this sense, this thesis hints towards the boundaries of contemporary research in the field of mental health.

# 2. The history of MDMA

## 2.1 Discovery and early usage

MDMA is a ring-substituted phenethylamine that was first synthesized by the German medical and pharmaceutical company *Merck KGaA*, Darmstadt in 1912 by Dr. Anton Köllisch (Benzenhöfer & Passie, 2006). However, it was only an intermediate during attempts to synthesize the antihemorrhagic agent Hydrastinine. While at the time no known applications were noted, the procedure to synthesize MDMA and related compounds was patented by Merck in 1914, according to the usual practice regarding new production methods and compounds. As opposed to the famous myth that MDMA was developed as an appetite suppressant – with a further myth being that the inventor was the notorious chemist Fritz Haber – MDMA was not pharmacologically tested until 1927, when MDMA's sympathomimetic effects were compared to adrenaline and ephedrine (Freudenmann, Öxler, & Bernschneider-Reif, 2006). In 1952 simple toxicological experiments were conducted and in 1959 a batch of MDMA was re-synthesized when interest in the production of new stimulants arose (ib.). However, in all these trials at *Merck*, MDMA remained a side note, and no evidence for any clinical trials can be found.
The first formal animal study applying MDMA – along with seven other related psychoactive substances – in five different species was conducted in 1953/54 at the University of Michigan. As the study was sponsored by the U.S. Military, which was interested in the potential of psychoactive substances as 'truth drugs', it remained classified until 1969 and was not published until 1973. This study provided comprehensive data on toxicology and behavioral effects (Hardman, Haavik, & Seevers, 1973).

As MDMA was identified in tablets seized in the streets of Chicago in 1970 (Gaston & Rasmussen, 1972), MDMA must have found its way outside research facilities and clandestine governmental laboratories, indicating that its effects on humans had become evident at that point. This event marks the end of the early history of MDMA and the

beginning of its diverse and controversial career as a substance both demonized and idolized.

## 2.2 Social and cultural history

The next chapter of the history of MDMA is inextricably linked with the name of the U.S.-based chemist and psychopharmacologist Alexander "Sasha" Shulgin. Shulgin had been concerned with the investigation of the chemistry and phenomenology of psychoactive substances since the late 1950s. The role of Shulgin, who was even dubbed 'the father of ecstasy', in the propagation on MDMA was surrounded for a long time by considerable speculation bordering historico-scientific lore. On the one hand, there are hardly any sources besides Shulgin's own accounts and on the other hand, much of the proceedings in those days were informal or even clandestine.[3] Following Shulgin's accounts and the research of Benzenhofer and Passie (2010), Shulgin *probably*[4] first synthesized MDMA in 1965 while working for *Dow Chemical* but did not investigate its psychoactive effects. It was not until 1976 that Shulgin was 'introduced' to MDMA by a student of medical chemistry and was apparently impressed by its effects (Shulgin, Shulgin, & Nichols, 1991; Stolaroff, 2004).
The first paper on the effects of MDMA in humans was published in 1978 by Shulgin and Nichols (1978). In this paper its 'psychotomimetic' effects were described as follows: "Qualitatively, the drug appears to evoke an easily controlled altered state of consciousness with emotional and sensual overtones." (p.4)

However, besides his research and publishing work, in 1977, Shulgin also clandestinely introduced the substance to psychologist and psychotherapist Leo Zeff at the U.S. West Coast. Zeff was apparently so "enraptured"(Stolaroff, 2004, p.18) by its therapeutically useful effects, that he abandoned his retirement and introduced it to many therapists across

[3] However, Shulgin's research and the psychoactive substances he investigated were *not* illegal at the time. But it is probable that with the increasing popularity of "ecstasy", Shulgin wanted to downplay his role in retrospect to protect his privacy (Benzenhofer&Passie, 2010).
[4] While Shulgin later suggested that he did so, there is no evidence in his laboratory notebook.

the U.S.. While these events undoubtedly mark the beginning of the history of MDMA as a medicine for psychotherapeutic application[5], it remains unclear how MDMA found its way to the streets as a recreational drug. Benzenhofer and Passie (2010) speculated that Shulgin himself was (unwittingly) responsible for the 'escape' of MDMA into the public, when in 1970 he described the synthesis to a colleague, who later provided access to this information to an underground chemist in the Midwest – where MDMA first appeared on the streets in the early 1970s.

While the apparent therapeutically useful effects of MDMA remained confined to the 'psychotherapeutic underground' for decades, all potential medical benefits were rapidly overshadowed by the long, steady, and global 'success story' of the street drug soon to be known as "ecstasy".

### *2.2.1 MDMA as a recreational drug or: the rise of "ecstasy".*

The style of this chapter is deliberately narrative – the field of illegalized psychoactive substances is strikingly underresearched; more precisely: for the greater part, existing research relies on a limited set of methods and perspectives on the field. Aggravatingly, even in peer reviewed papers the quality of studies, especially in regard to control over variables and generalizability, is often so unacceptable that I refrain from citing them. In conclusion, I often have to resort to evidence from field research, personal experience, and journalistic sources.

*Remark: "ecstasy" soon became extremely popular and its appearance had extensive and lasting cultural impact. In this context, the history of MDMA as a recreational drug can only be outlined. Yet it is necessary to understand the consequences of illicit use and abuse on the history and (contemporary) potential of MDMA as a therapeutic agent – after all, MDMA*

[5] See chapter 2.2.2

*transformed from a psychotherapeutic tool to a party drug. The influence of this 'cultural burden' on clinical research can hardly be overestimated.*

While MDMA was available on illicit markets as early as 1970, it took one decade, a rebranding, and the right (sub)cultural climate before it started to become a global phenomenon.

After the 1960s' psychedelic counter-culture movement with its propagation of 'mind-expanding' drugs had died down, heroin and especially cocaine became the more prominent drugs during the 1970s. As there was limited demand for a drug like MDMA[6], it was merely distributed among narrow circles of drug aficionados, often associated with the psychotherapeutic scene. However, at the beginning of the 1980s, a few enterprises in the United States realized the increasing commercial potential of the – at the time still legal – drug. In 1983, an enterprise in Texas began to professionally market the substance in bottled form via phone-order under the name "Sassyfras"[7] (Holland, 2001). It soon became available in nightclubs, sold over-the-counter – a development that did not go unnoticed by the Drug Enforcement Agency (DEA) (ib.).

While within the psychopharmacologist and psychotherapist circles MDMA carried the nickname "Adam"[8] or "Empathy"[9], a substance that was meant to be commercially successful in hedonistic scenes needed a label that was more catchy. Around 1981, a dealer came up with the suggestive name "ecstasy"[10] – a name that hit the *zeitgeist* (Holland, 2001; Parrott, 2004). The last necessary step towards a brand ready for mass dissemination was the manufacture of MDMA-containing pills, which made handling and dosing substantially easier. These pills, often bearing logos and/or pressed in recognizable forms became the symbol of "ecstasy" and an icon of the 1990s.

Some of the characteristic effects of MDMA[11] – such as feelings of empathy, closeness, love, strength, and heightened mood up to euphoria – resonated well with several emerging

[6] A substance that can rightly be called 'psychedelic' or 'mind-expanding'. See chapter 3.2
[7] Pun on "sassafras", a naturally occurring precursor of MDMA.
[8] Leo Zeff came up with this nickname (Stolaroff, 2004, p.86), hinting at „the condition of primal innocence and unity with all life"(Adamson & Metzner, 1988) he believed its subjective effects may resemble.
[9] MDMA actually became the prototype of a new class of psychoactive substances, the 'empathogens' – a term coined by clinical psychologist Ralph Metzner in 1985 (personal communication, September 19, 2013)
[10] Commonly abbreviated "XTC", „E" or „X"
[11] See chapter 3.2

subcultures during the 1980s. “Ecstasy” hit scenes more likely to adopt it quickly, such as the gay club scene of New York City (and subsequently the associated European scenes) and various esoteric cults, as well as relatively unexpected scenes such as the football hooligan scene in the UK (Gilman, 1994); however, the scene which “ecstasy” certainly shaped and influenced like no other was the electronic music scene.

The rave-movement, one of the predominant subcultures during the late 80s and throughout the 90s, cannot be understood without the crucial influence of “ecstasy”. In short: rave *was* “ecstasy” and repetitive electronic music, celebrated by masses of people (cf. Reynolds, 1998). The seed was planted on Ibiza in the years following the summer of 1986 where the first MDMA-fueled raves took place and after which their participants brought the idea of ‘rave’ back to their home-countries (Holland, 2001). Within the following years, rave and associated “ecstasy” use became a mass phenomenon across Europe with hundreds of thousands of pills consumed every weekend. The phenomenon would soon be exported to the United States – and around the world.

Until the mid-1990s, MDMA – in the manifestation of the party drug “ecstasy” – had been spilling across the Atlantic Ocean and back again. This of course was long after MDMA was classified as a ‘Schedule I’ illegal substance[12] in the U.S., which marked the preliminary end of MDMA as a potential therapeutic agent.

Facing increasing “ecstasy” abuse in the early 1980s coupled with the potentially toxic effects of the substance[13], the DEA was determined to take drastic measures. Despite organized opposition by proponents of MDMA’s therapeutic value[14] and public controversy, MDMA – and any clinical application – was temporarily but effectively banned in 1985 (cf. Shulgin, 1986). This controversy extended until 1988 when a permanent ban took effect. However, the influence of U.S. authorities led the World Health Organization to place MDMA on Schedule I of the 1971 Convention on Psychotropic Substances in 1986.

[12] A substance with high potential for abuse, no currently accepted medical use and lack of accepted safety for use under medical supervision.

[13] The potential toxicity of the closely related and already scheduled compound MDA had been demonstrated before.

[14] No randomized controlled trials had been conducted to support that claim.

The WHO (World Health Organization) Expert Committee on Drug Dependence noted in their report:

> The Expert Committee held extensive discussions concerning therapeutic usefulness of 3,4 Methylenedioxymethamphetamine. While the Expert Committee found the reports intriguing, it felt that the studies lacked the appropriate methodological design necessary to ascertain the reliability of the observations. There was, however, sufficient interest expressed to recommend that investigations be encouraged to follow up these preliminary findings. To that end, the Expert Committee urged countries to use the provisions of article 7 of the Convention on Psychotropic Substances[15] to facilitate research on this interesting substance.

A footnote reflects that a controversy did also occur within the board of the WHO:

> One member, Professor Paul Grof (*Chairman*), felt that the decision on the recommendation [to place MDMA in Schedule I] should be deferred awaiting, in particular, the data on the substance's potential therapeutic usefulness and that at this time international control is not warranted. (*WHO Expert Committee on Drug Dependence: Twenty-second Report*, 1985, p.25)

Due to international treaties, this recommendation led to the obligatory international illegalization of MDMA.[16]

While the prohibition of the substance virtually ended clinical research[17], it evidently did not hinder its mass dissemination as a recreational drug. The widespread uncontrolled consumption inevitably took its toll: Severe and sometimes fatal intoxications[18] caused by overdoses as well as a number of 'E-victims' presenting themselves in psychiatrists' offices with mental problems following heavy "ecstasy" abuse. These acute cases, together with growing evidence of MDMA's long-term neurotoxic effects and the notion of a youth

[15] Article 7 regulates government authorized use of Schedule I substances for scientific or medical purposes.
[16] In Germany, the „Zweite Betäubungsmittelrechts-Änderungsverordnung" added MDMA to Anlage 1 of the German Betäubungsmittelgesetz on 1st of August 1986. Since then it is non-tradeable without a special permission by the "Bundesinstitut für Arzneimittel und Medizinprodukte".
[17] N.B.: it was not made technically impossible to conduct clinical research with MDMA – but extraordinary administrative and political barriers and social stigma produced a marked effect.
[18] See chapter 3.4

movement that seemed out of control, lead to (recurring) moral panics in many affected countries (cf. Critcher, 2000; Rosenbaum, 2002). MDMA became an illicit substance that was heavily targeted by law enforcement agencies and the mass media alike.
Aggravatingly, and following the rules of the market, "ecstasy" was less and less equivalent with MDMA. 'Pills' commonly contained and contain a range of random stimulating and/or empathogenic substances or concoctions – with unpredictable effects and risk profiles. The amount of MDMA in "ecstasy"-pills varies widely (ranging from none at all to potential overdoses) and is subject to considerable fluctuations (Vogels et al., 2009), apparently depending on the availability of precursors on the global market and the efficacy of customs authorities. Eventually, these insecurities have led to the dissemination of qualitative 'test kits' and the development of the secondary prevention method of 'drug checking'. 'Drug checking' is an in-field-method that combines rapid qualitative and quantitative chemical analysis of the substances clients plan to consume, followed by counselling and associated data collection (Kriener et al., 2001; Schroers, 2002).

During the last years, the unbroken demand for MDMA – or more accurately: its effects profile[19] – has led to the appearance of "ecstasy" in the form of seemingly 'pure' crystals, branded Molly (in the U.S.) or Mandy (in the UK). Of course – as is the nature of an unregulated market – these crystalline compounds can and do still contain literally *anything*. However, this development led to a public revival of MDMA and to new groups of consumers, who often regard "Molly" as a new product, unrelated to "ecstasy" or MDMA and associated risks.

This recent trend aside, the connection of electronic music and "ecstasy" has remained unbroken during the last 25 years. Besides the original scenes in which the "ecstasy"-phenomenon grew to global popularity (e.g., rave and the gay scenes), "ecstasy" plays a crucial role in many other alternative scenes such as the psychedelic trance, the clubbing scene or on so called transformational festivals (cf. Bottorff, 2015).

Today "ecstasy" remains one of the most popular illicit psychoactive substances: in 2009 the 12 months prevalence in Germany for persons aged 15-64 was 0.4%, the lifetime prevalence

[19] Dozens of pharmacologically and phenomenologically more or less comparable substances have been developed and marketed with the sole purpose to skim the "ecstasy"-market while evading legislation for at least a short period of time.

was at 2.4% (EMCDDA, 2013); the UNODC estimates the world wide lifetime prevalence of "ecstasy" use in 2011 at 19,4 million or 0.4% of the world population (UNODC, 2013).

Given its history as a recreational drug, MDMA carries a high level of stigma as well as mystification with it. Any research project utilizing MDMA in humans will have to take into account the specific social and political implications that are associated with the recreational, uncontrolled, and illicit use of the substance.

### *2.2.2 Utilization of MDMA as a therapeutic agent*

There are estimates that Leo Zeff – after Shulgin pointed him to the potentially therapeutic usefulness of MDMA – introduced no less than 4000 therapists to the substance during the 1970s and early 80s (Holland, 2001, p.12; Shulgin et al., 1991; Stolaroff, 2004 p.18). However, the application of MDMA remained clandestine; researchers and therapists had learned from the disillusioning experiences of the 1960s.

During the 1950s, another class of psychoactive substances had seen a short but promising career in research as potential adjuncts to psychotherapy; for a short period of time, psychedelic substances like LSD, mescaline, and psilocybin seemed to initiate a new paradigm in psychiatry (cf. Hofmann, 2013).[20] However, and this was completely unforeseen by medical professionals (ib.), the extremely potent psychopharmacological agent LSD was 'set free' from the clinical context, fueled the movement of 1968 that threatened traditional values, hit an unprepared and vulnerable mainstream and was subsequently demonized (cf. Stolaroff, 2004, p.21f.) – ending clinical research until 2014, when Gasser et al. (2014) published a psychotherapeutic study applying LSD.
As a consequence, MDMA did not find its way into academia but was used discreetly. While

[20] During this period the invention of chlorpromazine introduced the first effective (pharmacological) intervention for psychotic disorders and fueled hopes for a neuropsychopharmacological revolution in psychiatry (Ban, 2007). In this context it can be argued that the newly invented neuroleptics were to "psychoses" what LSD and related substances were to "neuroses"(cf. Unger, 1963).

this precaution preempted formal research[21], it did not stop MDMA from becoming so widely distributed that it became a public health concern.
With the illegalization of MDMA, research on its psychotherapeutic potential came to an overall halt. At the same time, its use as a recreational drug resulted in a vast amount of research focusing solely on the toxicology and pathogenetic aspects of the uncontrolled consumption of "ecstasy".[22]

Nevertheless, MDMA has been continuously used for therapeutic motives in formal and informal, legal and illegal, professional and nonprofessional settings since the mid-1970s. While therapeutic trials have only been conducted during the last decade (Bouso, Doblin, Farré, Alcázar, & Gómez-Jarabo, 2008; Mithoefer et al., 2011; Oehen, Traber, Widmer, & Schnyder, 2013), the more or less clandestine use resulted in a plethora of anecdotes and case descriptions.

The next paragraphs will address this part of MDMA's history.

a) Formal and informal settings

There are no scientific papers on the early therapeutic use of MDMA in *formal settings.*[23]
The first systematic account of MDMA's effects in a clinical setting comes from psychiatrist and psychotherapist George Greer (Greer & Tolbert, 1986), who had been legally working with MDMA since 1980 (Holland, 2001, p.223). However this study was exploratory. It was deliberately unblinded, unstructured, and devoid of planned therapeutic interventions; yet it put forward the first detailed phenomenological description of the subjective effects of varying doses of MDMA in 29 diverse subjects with different motives. The authors report apparent physical safety, no serious side effects and positive and sometimes lasting psychological benefits in most of the subjects. Those included "reported significant benefit" (p.326) in all 9 subjects with diagnosed psychiatric disorders, with 2 of these reporting

[21] "We were therapists using a substance in therapy, not university or institutional researchers with funding support." (Ralph Metzner, personal communication, September 19, 2013)
[22] N.B.: The majority of the publications regarding "ecstasy" is unsuitable in an attempt to judge the risks and potentials of MDMA in clinical settings. (cf. Cole & Sumnall, 2003a; Krebs & Johansen, 2012)
[23] Anecdotal examples will be presented in Chapter 2.3

"lasting remissions" (ib.). The authors speculate about therapeutic efficacy in psychosomatic conditions, in conjoint settings, in insight-oriented psychotherapy, and in the treatment of substance abuse. They encourage further research while stressing the limits of MDMA's usefulness and discourage the notion of MDMA as a "social or psychological panacea" (ib.).

Several randomized controlled clinical studies applying MDMA to investigate the mechanisms of its therapeutic potential have been conducted since the ban (cf. Bedi, Hyman, & de Wit, 2010; Carhart-Harris, Kevin, et al., 2014; Carhart-Harris et al., 2013; Dumont, Sweep, et al., 2009; Grob, Poland, Chang, & Ernst, 1995; Vollenweider, Gamma, et al., 1998; Vollenweider, Liechti, Gamma, Greer, & Geyer, 2002), however all of those studies dealt with healthy volunteers and did not directly check for therapeutic efficacy.

Up to now, the only sanctioned application of MDMA in regular psychotherapy was conducted by therapists organized in the *Schweizerische Ärztegesellschaft für Psycholytische Therapie*[24] (SÄPT) who obtained an exceptional permission to work with MDMA and LSD between 1988 and 1993. Unfortunately, scientific evaluation was neglected during those trials, there is merely a catamnestic study including retrospective reports of 170 former patients. The data obtained and the methods used are unsuitable to draw conclusions about therapeutic efficacy of MDMA, however after therapy 90,9% of patients reported "slight or thorough improvements" and – more important – no case of psychiatric hospitalization, psychotic decompensation, or suicide was reported, suggesting that paradigms applying psychoactive substances in therapy are sufficiently safe (Jungaberle, Gasser, Weinhold, & Verres, 2008, p.348).

In the United States the Multidisciplinary Association for Psychedelic Studies (MAPS) was founded in 1986 to promote clinical research on the therapeutic potentials of psychoactive substances (Emerson, Ponté, Jerome, & Doblin, 2014). Currently, the organization focuses on collecting the data necessary to make MDMA an approved therapeutic agent (ib.). As yet, these efforts resulted in three randomized controlled trials with MDMA in the treatment of PTSD (Bouso, Doblin, Farré, Alcázar, & Gómez-Jarabo, 2008; Mithoefer, Wagner, Mithoefer,

[24] Swiss Medical Society for Psycholytic Therapy

Jerome, & Doblin, 2011; Oehen, Traber, Widmer, & Schnyder, 2013). The available results are promising and safety was demonstrated.[25]

Given the necessarily clandestine nature of the use of MDMA in *informal settings* there are no systematic data. However, it can be assumed that the phenomenon is certainly not rare. Liester, Grob, Bravo, and Walsh (1992) presented a study with retrospective accounts of 20 psychiatrists who self-experimented with MDMA; Weinhold (2010) presented a sample of 20 physicians and psychotherapists who used psychoactive substances (including MDMA) informally for self-experience and professional (self-)improvement.
However, there are no credible studies concerning illicit application of MDMA in psychotherapy by professionals – legal risks and potential social stigma keep such practices in the underground. Passie and Dürst (2009) presented extensive qualitative data on psycholytic sessions applying MDMA, without disclosing the circumstances where those sessions took place. It is evident that those sessions were not sanctioned.

It is obvious that some therapists who had been using MDMA for the treatment of mental health disorders before it was banned and were convinced of its efficacy, did not stop applying it to patients. Shulgin et al. (1991) quote a psychiatrist: “MDMA is penicillin for the soul and you don't give up penicillin once you've seen what it can do” (p.74).
Although there are no data on this topic, it can be assumed that there are numerous therapists world-wide who are willing to conduct MDMA-assisted sessions clandestinely or in a ‘grey area’.[26]

b) Self-medication and self-treatment with MDMA

Although MDMA has a reputation as a stimulating and euphoriant party drug, many people seek out its effects to deal with various mental and somatic ailments.

[25] See chapter 6
[26] I am personally aware of therapists who would not personally handle illicit substances and take responsibility for their use but would still supervise experiences brought on by those substances and help integrating them in a therapeutic process.

Beck (1994) identified a "therapeutic-recreational continuum" (p.60) regarding the motives of MDMA use. At one end of the spectrum therapeutic benefits or personal growth, on the other end fun and partying are the reasons for using MDMA. According to Beck's interview-study, the vast majority of users lie somewhere in between the two extremes; even the most therapeutically inclined users experience 'euphoric or sensual enjoyment' and 'hard-core partiers' attribute long-term improvements of interpersonal skills to MDMA use. Therapeutic motives should not be seen as fundamentally incompatible with hedonistic experience and vice versa. Unsurprisingly, expectations and motives of MDMA use shape the nature of the experiences themselves (cf. Sumnall, Cole, & Jerome, 2006), the (long-term) outcomes and perceived importance.[27]

*What are reasons for self-treatment with MDMA?*

The U.S.-American non-profit organization "Erowid" is concerned with psychoactive substances and altered states of mind.[28] An online section with first-person experience reports (cf. Erowid, 2006) provides a convenient opportunity to scan for examples of self-medication with MDMA. In the sub-section "Health Benefits"[29] the following 'indications' were identified:

PTSD, repressed traumatic memories and sudden recollection (e.g., childhood abuse), depression, schizophrenia, bipolar disorder, OCD, autism, drug addiction, adolescent crisis, existential crisis, sexual dysfunction, anorexia, bulimia, bereavement, social anxiety.

Notably, many reported the 'therapeutic effects' occurred spontaneously, to the surprise of the users and the 'indication' was determined post-hoc. However, most of the reports don't describe acute pharmacological effects but effects resulting in long-term adaptive personality changes.

[27] See the 'drug, set, and setting'-approach by Zinberg (1984)
[28] Self-description: "Erowid is a member-supported organization providing access to reliable, non-judgmental information about psychoactive plants, chemicals, and related issues. We work with academic, medical, and experiential experts to develop and publish new resources, as well as to improve and increase access to already existing resources. We also strive to ensure that these resources are maintained and preserved as a historical record for the future." (Retrieved from http://www.erowid.org/general/about/about.shtml)
[29] http://www.erowid.org/experiences/subs/exp_MDMA_Health_Benefits.shtml

Accounts of more functional or intentional self-medication with MDMA deal with relationship issues, creativity enhancement, seasonal affective disorder, relief of chronic pain, migraine, stutter, or cerebral palsy.
The aforementioned lobby organization MAPS also displays a collection of reports[30], where MDMA's effects were perceived as beneficial, complementing the following indications: Palliative care and end of life anxiety, Parkinson's disease, rheumatoid arthritis.

*Anticipatory side note:*

In the light of this wide range of self-reported psychiatric indications, where MDMA might potentially have been effective, a characteristic property of MDMA – as well as other therapeutically applicable psychoactive substances – becomes evident: unlike classic psychiatric medications, substances such as MDMA do not exclusively develop therapeutic efficacy via a specific psychopharmacological mode of action and a clear and causal dose-response-relationship. They rather open an unspecific possibility space for psychological processes to take place (see chapter 5).[31]

Today, Beck's research has apparently not lost its actuality. Across the internet, there are plenty of accounts of laymen who use MDMA deliberately and purposefully, knowing about its potentially therapeutic effects. Those users treat experiences induced by MDMA rather as a complement or an alternative to formal psychotherapy. Another prominent motive is spiritual and/or personal growth and relationship work – MDMA is then regarded as a 'psychological tool' in often self-structured or even ritualized self-experience sessions.
On the other hand, there are also numerous accounts of people who were originally interested in the recreational effects of MDMA[32], but who unintentionally and unexpectedly discovered effects they consider beneficial for their well-being. Such 'discoveries' may remain isolated incidents. Yet in some cases they can also switch the motives to use the

[30] Retrieved from http://www.maps.org/mdma-research-timeline/168-other-mdma-resources/resources-on-the-maps-site/366-accounts-of-mdmas-healing-effects
[31] Efficacy in (more) somatic indications is an exception as there are clear pharmacological modes of action. E.g., MDMA's dopaminergic activity in Parkinson's disease.
[32] N.B.: Predominantly recreational use is trivial in this context.

substance towards the therapeutic end of the spectrum. As MDMA is predominantly regarded as a recreational drug of *ab*use, scientific literature on the prevalence of quasi-'therapeutic' use and possible integrative and/or adaptive processes within users of MDMA is lacking. [33]

On the scale of public health, there is empirical evidence that childhood symptoms of anxiety and depression lead to an increased tendency to use MDMA as a form of self-medication (Huizink, Ferdinand, van der Ende, & Verhulst, 2006). Moonzwe, Schensul, and Kostick (2011) stressed the function of MDMA use as a coping mechanism in situations of abuse, relationship conflicts, loss, and more general lifestyle stresses related to socioeconomic insecurity – this function was visible *only* in persons that were not diagnosed with mental health problems or persons that were diagnosed but unsatisfied with their treatment. It is noteworthy that MDMA use in this function does not aim for personality growth or increased long-term resilience but serves a 'palliative' purpose of numbing and forgetting; it merely substitutes appropriate mental health care. This phenomenon can be regarded as a nonreflecting form of self-medication.

### *2.2.3 Myths and public image of MDMA*

"An unusually large amount of commentary and opinion has appeared in the popular press and in both professional as well as lay journals. Occasionally there may be some statements of fact, but usually there is much misstatement of fact" (Shulgin, 1986, p.301).

Shulgin made this statement on the public dialogue around MDMA during the time when it was to be illegalized. Generally it still holds true today. The potentials of its therapeutic use on the one hand and the dangers of its abuse, its illegalization and condemnation in

[33] From a perspective of sociology of science this is not a surprising fact but a direct consequence of funding policies that support the (prohibitionist) status quo in drug legislation.

academic contexts on the other led to a distinct split-up of the discourse into two opposing positions.

The extreme proponent-position sees MDMA as a "social or psychological panacea"(cf. Greer & Tolbert, 1986), a "magic bullet" or even a "sacrament", disregarding inherent limitations and dangers. There is no evidence that this position was ever held by health professionals and/or academic psychotherapists concerned with MDMA as an adjunct in psychotherapy – this notion can be regarded as an urban myth created by early recreational MDMA users; in a broader sense it may serve as a justification of potentially maladaptive MDMA use.

The early MDMA-researcher Ralph Metzner states:

> "I never said or implied, nor do I think now, that MDMA in any way represents a "magic bullet". It is simply the best adjunct to psychotherapy, in my view. The fact that the drug is also used in rave dance parties, where the purpose is not at all therapeutic, simply confirms that the set and setting hypothesis applies here as well.[34]"(personal communication, September 19, 2013)

This quote hints to two areas of attack for the other extreme position on MDMA: While the 'straw man' of imprudent and missionary MDMA-apologists[35] provides one target, uncontrolled and potentially maladaptive use as a recreational drug is a more efficient target for attack. The *deviant* setting of rave parties with a set desiring literal ecstasy by the primary means of reckless consumption of MDMA invited mass media attention as well as academic alarmism. The apparent dangers of MDMA – or furthermore: 'the MDMA-epidemic' – were soon inflated towards irrational demonization. One distinct point of culmination was a paper by Ricaurte, Yuan, Hatzidimitriou, Cord, and McCann (2002) published in the leading journal *Science* and linking MDMA to Parkinson's disease. This article gained notoriety because – as it turned out – its findings relied on mysteriously mixed up research materials.[36] It represents one of the few retracted articles in that journal and put fundamental issues about the credibility of government funded drug research on the

[34] Metzner refers to research by Zinberg (1984) and disregards the therapeutic-recreational continuum proposed by Beck (1994).

[35] An unfounded but recurring phrase in dedicated 'anti-ecstacy' papers is that the drug is "regarded as safe" by its users. See Gamma, Jerome, Liechti, and Sumnall (2005) for a rebuttal of this statement.

[36] The much more potent and toxic compound methamphetamine was used instead of MDMA.

agenda of the scientific community (cf. "Ecstasy's after-effects," 2003). Said government funded drug research also supported ‘advertising campaigns’ depicting “ecstasy” as an agent that creates actual holes in brain tissue – with the apparent aim of creating a drastic narrative for influencing public risk assessment. Both of these untenable instances helped shape the public image of “ecstasy”-consumption as an extraordinarily hazardous venture. Uncontrolled consumption of MDMA does bear acute and chronic risks and an unfortunate series of events may even lead to fatalities. On the other hand, sensationalism and alarmism in mass media and academia alike helped cloud a rational view on the objective risks of MDMA use and ways to minimize those risks.[37] When Nutt (2009) – provocatively – compared the objective risks of horse-riding (1 instance of acute harm to person in 350 episodes) with those of “ecstasy”-consumption (1 instance of acute harm to person in 10000 episodes), it did not lead to a public debate but to his dismissal as chairman of the government’s Advisory Council on the Misuse of Drugs in the United Kingdom.

Whether MDMA is perceived as a catastrophic and quasi-contagious ’one pill can kill’-brain toxin or a miraculous panacea: it is obvious that in this field the line between unbiased research and ideology, between information and propaganda is small and thus the public image of MDMA – as well as other illicit psychoactive substances – is corrupted by myths and misinformation.

A public stance that holds some truth considering the MDMA phenomenology, is the notion of MDMA as a ‘love drug’. Increased sociability, emotional closeness, and sensuality are indeed core elements of the MDMA experience, however MDMA is no aphrodisiac and no ‘sex drug’ – on the contrary: in many subjects it does actually impair sexual drive and functioning during its peak effects (cf. Passie, Hartmann, Schneider, Emrich, & Krüger, 2005).

Another misconception about MDMA comes from its seemingly stimulant nature and its connotation with the rave scene – it seems blatantly unlikely that such a substance could be

[37] In a study by Forsyth (2001) Scottish newspapers displayed a systematic bias in reporting drug fatalities over the course of one decade: While fatalities involving legal psychoactive pharmaceutical drugs were responsible for the majority of drug deaths they were rarely reported, while *every* fatality involving MDMA was reported. The author concludes: “[…] it may be argued that these deaths only receive the greatest attention because they are so rare, and therefore literally newsworthy, it must be contended that there is a danger that this creates an unrealistic perception of drug problems. Such unbalanced representations may be transmitted to the minds of the public, policy makers and novice drug users, with potentially harmful consequences.” (p.450)

useful for psychotherapy. While it is chemically related to classic psychostimulants (most closely: methamphetamine) and displays some properties of stimulants in its pharmacology, MDMA does not necessarily induce stimulant (side-)effects like increased locomotion and anxiety but rather a unique and seemingly paradox equilibrium of stimulation and relaxation[38] – which of those properties dominates the individual experience is determined by set and setting. MDMA may provide feelings of boundless energy for ravers as well as feelings of deep relaxation and serenity in a therapeutic setting.

Today the 'party drug' discourse still dominates the public perception of MDMA. Besides the either glorifying or demonizing "Ecstasy"-, "Molly"- or "Mandy"-craze – depending on region and era – there is not much room for the notion of MDMA as a psychopharmaceutical adjuvant in psychotherapy.

[38] These unique effects have led to the introduction of a new group of psychoactive substances: the empathogens or entactogens.

# 3. The effects of MDMA

## 3.1 Neuropsychopharmacology

Despite MDMA being an illicit psychoactive substance, the pharmacology and neuropsychopharmacology is relatively well researched, especially in vitro and in animal models (cf. Green, Cross, & Goodwin, 1995), but the state of knowledge about MDMA's effects in humans has also distinctly improved during the last 15 years. It is unclear to which extend insights from animal models can be generalized to humans; this is not only true for behavioral and psychological effects, but also for more basic matters like metabolism, dose-response relationship, toxicity, and neuropharmacology (Green, Mechan, Elliott, O'Shea, & Colado, 2003; Vollenweider, Jones, & Baggott, 2001). It is therefore sensible to focus on clinical studies investigating the effects of MDMA in humans, even if there is quantitatively less evidence.

As a phenethylamine, MDMA has structural similarities with dopamine (3,4-dihydroxyphenethylamine); see Figure 1:

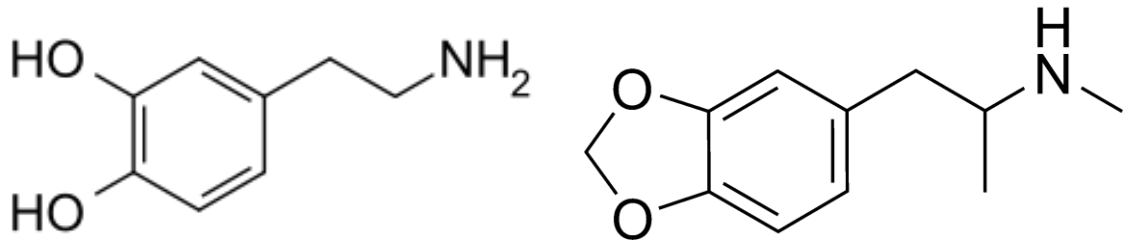


*Figure 1. The structural formulae of dopamine and MDMA (retrieved from: http://commons.wikimedia.org)*

In vivo MDMA directly increases extracellular concentrations of the monoamine neurotransmitters serotonin (5-HT) (Nichols, Lloyd, Hoffman, Nichols, & Yim, 1982), – and to a lesser extend (Liechti & Vollenweider, 2001) – dopamine (DA) (Koch & Galloway, 1997) and norepinephrine (NE) (Fitzgerald & Reid, 1990). The main mechanisms involved are increased

intraneuronal synthesis, reuptake inhibition, monoamine oxidase inhibition, and carrier-mediated exchange; MDMA also displays moderate affinity to various receptors including serotonergic, histaminergic, and muscarinergic receptor sites (Cole & Sumnall, 2003b).

MDMA's action on the serotonin-transporter (SERT) and 5-HT concentrations is responsible for most of the distinct psychological effects (Liechti, Baumann, Gamma, & Vollenweider, 2000), action on DA concentrations is responsible for the positive mood/euphoria associated with MDMA consumption (Hysek, Simmler, et al., 2012; Liechti & Vollenweider, 2000). The mild hallucinogenic effects of MDMA (perceptual changes, emotional excitation) are mediated via the 5-$HT_2$ receptors (Liechti, Saur, Gamma, Hell, & Vollenweider, 2000), while the stimulant-like effects are produced by MDMA's influence on NE concentrations (Hysek et al., 2011). It shows significant agonist actions at the alpha2-adrenoreceptor (Lavelle, Honner, & Docherty, 1999); relaxing and antihypertensive effects can be attributed to this action.

Today many of the complex direct and indirect actions and interactions between MDMA and the neurotransmitter systems remain poorly understood. Especially the neurochemical mechanisms that underlie the prosocial or empathogenic effects of MDMA are largely unexplored (Hysek, Domes, & Liechti, 2012). The affinity of MDMA to the 5-$HT_{1a}$-receptor is of special interest as there is sufficient evidence to argue that many of the unique pro-social effects of MDMA are mediated via this receptor.

*Neuroendocrine effects*

MDMA administration affects the hypothalamic-pituitary-adrenal (HPA) axis and increases plasma levels of adrenocorticotropic hormone (ACTH), cortisol, dehydroepiandrosterone (DHEA), prolactin, and arginine vasopressin (AVP) (Cole & Sumnall, 2003b; Harris, Baggott, Mendelson, Mendelson, & Jones, 2002).

*MDMA and Oxytocin*

Researchers have long been puzzled by the underlying psychopharmacology of MDMA's

distinctive pro-social effects[39] – structurally and pharmacologically similar substances, e.g., amphetamine, do not possess those effects.

Today there is evidence to conclude that some of the empathogenic effects are induced by the release of the 'social neuropeptide' oxytocin (OXT) (cf. Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005; Lee, Macbeth, Pagani, & Young, 2009; Neumann, 2008). In rats, the prosocial effects of MDMA (cf. Morley & McGregor, 2000) are prevented when a selective 5-$HT_{1a}$-receptor antagonist (Morley, Arnold, & McGregor, 2005) is co-administered, MDMA and its metabolites release AVP and OXT in dissected rat thalami (Forsling et al., 2002), and co-administration of a 5-$HT_{1a}$-receptor-antagonist decreases *both* OXT release and prosocial effects (Thompson, Callaghan, Hunt, Cornish, & McGregor, 2007).
Human recreational users of MDMA also show increased OXT concentrations (Wolff et al., 2006). In a controlled clinical trial, MDMA increased blood OXT concentrations; moreover the (positive) correlation of OXT concentration and prosocial feelings was stronger than the correlation of MDMA concentration and prosocial feelings (Dumont, Sweep, et al., 2009).

The link between MDMA's action on the 5-$HT_{1a}$-receptor, OXT-release, and prosocial effects is therefore well-established (Carson, Guastella, Taylor, & McGregor, 2013; Emanuele, Arra, & Pesenti, 2006). However, while OXT plays a crucial role in the uniqueness of the MDMA-phenomenology, the effects are not sufficiently explained by OXT but rather emerge from the complex interplay of psychopharmacological actions.

[39] See chapters 3.2.1 and 3.4

## 3.2 Pharmacology

a) Pharmacodynamics

MDMA is catalyzed in the liver by debrisoquine 4-hydroxylase (CYP2D6) and catechol-O-methyltransferase (COMT), large amounts of MDMA are excreted in the urine (Cole & Sumnall, 2003a; De la Torre et al., 2004). Figure 2 shows the metabolic pathways of MDMA. Interestingly, the minor metabolite 3,4-Methylenedioxyamphetamine (MDA) represents 8-9% of MDMA concentrations and is also psychoactive.

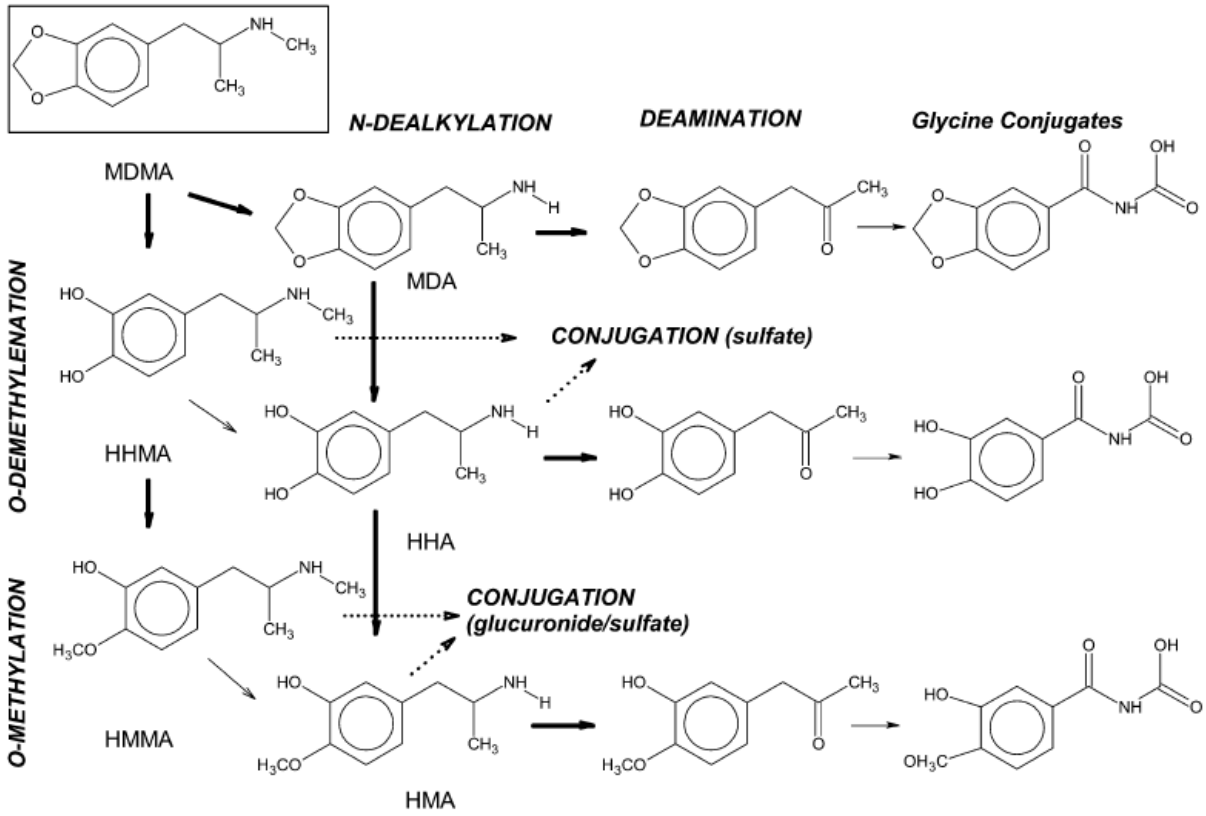


*Figure 2. Metabolic pathways of MDMA (De la Torre et al., 2004).*

b) Pharmacokinetics

Serum levels of MDMA peak 2h after administration, the elimination half-life is 8h (Cole & Sumnall, 2003a). The pharmacokinetics are nonlinear: increased doses lead to

disproportionately increased peak concentrations. This is probably due to the formation of a metabolite-enzyme complex[40]; thus MDMA blocks its own metabolism.

For practical reasons, Figure 3 shows the time course of the *subjective* (and not the pharmacological) effects of placebo, 0.5mg/kg [J] or 1.5mg/kg [H] of MDMA.

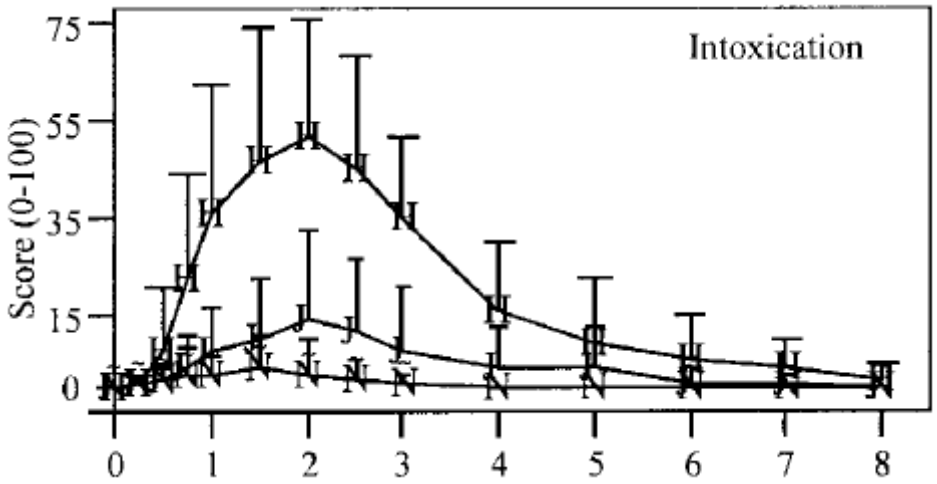


*Figure 3. Time course for subjective measures of intoxication by MDMA (Harris et al., 2002).*

In a therapeutic setting, the following time course was reported: "Onset of MDMA effects occurred 45–75 minutes after the application of the initial dose. The effects reached a peak at 2–2.5 hours and lasted 4–5 hours in the […] subjects who received a single dose, and 5–6h in those […] who received a supplemental dose.[41] Effects diminished gradually over several hours." (Mithoefer et al., 2011, p.445)

[40] In higher doses, this effectively disables this enzyme (CYP2D6), resulting in increased toxicity with repeated doses as well as potentially fatal interactions with other pharmacologically active substances; see chapter 3.3.4.
[41] 50% of the initial dose. Specifically applied to prolong the effects.

## 3.3 Phenomenology

When discussing the effects of psychoactive substances, it is crucial to understand that the phenomenology is *not* determined by the pharmacological properties of the substance in question – this is particularly true for substances with psychedelic properties. This issue entails a plethora of scientific peculiarities and will be discussed in chapter 7. For now, I want to acknowledge the observation by Sumnall et al. (2006):
"In studying the consequences of taking MDMA/ecstasy we are probably describing the interaction between social history, and psychopharmacology […], environmental context, use function, effect expectancies and individual personality traits." (p.680)

### *3.3.1 The psychological effects of MDMA*

MDMA shares properties of psychostimulants, such as amphetamine, and classic psychedelic substances, such as LSD and psilocybin, but was soon recognized as the lead compound of an entirely new class of psychoactive substances. It was first classified as an "empathogen" – a substance that induces feelings of empathy – by psychotherapist Ralph Metzner in the early 1980s (personal communication, September 19, 2013), then as an "entactogen" (Nichols, 1986; Nichols & Oberlender, 1990) – a substance enabling to get 'in touch'. Today the terms empathogen and entactogen are largely interchangeable, however entactogen is more common in the scientific literature.

Similar to classic psychedelic substances, empathogenic substances intensify sensations. However, they differ from psychedelics in that they produce no or limited perceptual alterations or imagery. The scope of those substances is less oriented on ideation and cognition as it is on emotional contents, empathy, and sensuality – a feature that also distinguishes them from psychostimulants. While loosening ego boundaries, empathogens don't lead to ego-disintegration and impairment of ego functions that is typical for (high-dose) psychedelics (cf. Nichols, 1986; Vollenweider et al., 2002).

Moreover, although MDMA has some psychedelic effects, the pharmacological and subjective effects are – unlike classic psychedelics – consistent across *clinical* settings (Kirkpatrick, Baggott, et al., 2014). This indicates that the effects are less susceptible to environmental and individual factors and are therefore relatively predictable under sufficiently controlled circumstances.

In controlled clinical settings, a typical dose of MDMA (1.7mg/kg) produces an affective state of enhanced mood, (profound) well-being, happiness, (physical and mental) relaxation, increased emotional sensitiveness and responsiveness, little anxiety (mainly during the come-up phase), unique anxiolysis (see chapter 3.3.3), heightened openness, sociability, extroversion, and a sense of closeness to other people. Spatial and temporal orientation is maintained, however subjects may feel dreamy or lost in thought. Depersonalisation and/or derealization phenomena are slight-to-moderate, not accompanied by anxiety and not experienced as problematic. Psychomotor drive is not markedly stimulated. Perceptual changes are usually limited to minor disturbances such as: intensification of light, colors, sounds, touches, and seeing flashes of light or simple patterns; full-fledged hallucinogenic effects are uncommon and more frequent with increasing doses (Harris et al., 2002; Vollenweider, Gamma, et al., 1998; Vollenweider et al., 2002; Vollenweider, Liechti, & Paulus, 2005).

In some trials, MDMA produced stronger effects in women than in men (Hysek et al., 2014; Liechti, Gamma, & Vollenweider, 2001). Reviewing several clinical studies, Kirkpatrick, Baggott, et al. (2014) did not observe this effect, however it should be further investigated as potential gender differences will have to be considered in future therapeutic trials.

To assess the subjective effects of MDMA, Vollenweider, Gamma, et al. (1998) used the *Abnormal Mental States questionnaire APZ-OAV* (Dittrich, 1998) (Figure 4):

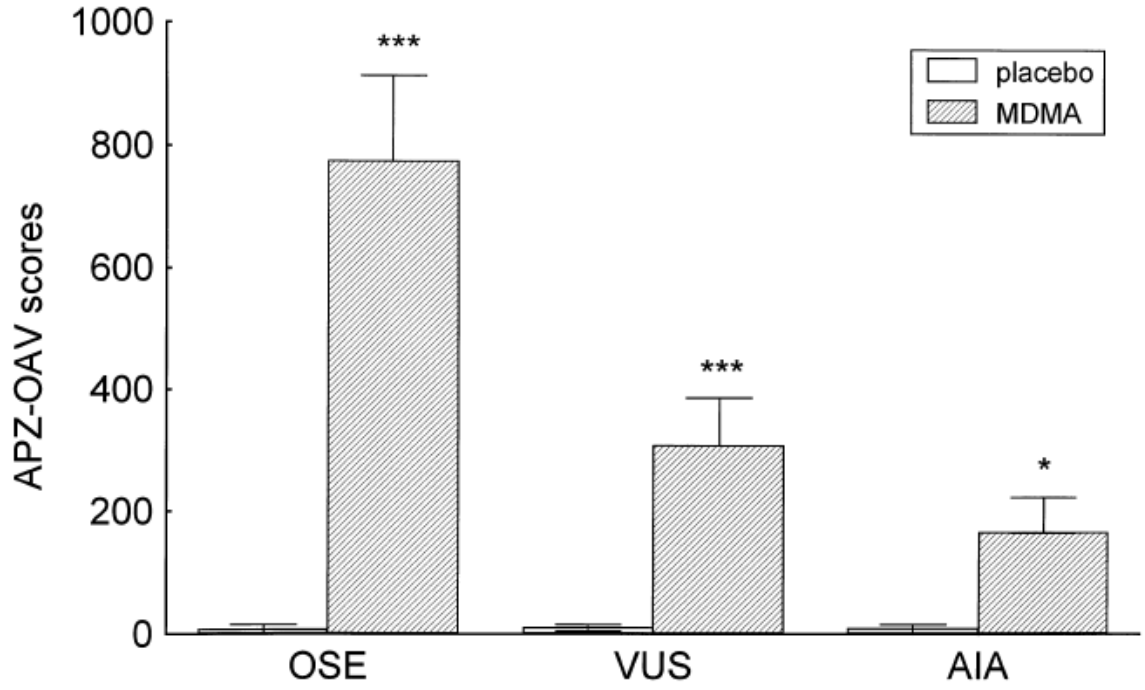


*Figure 4. APZ-OAV scores of 1.7mg/kg MDMA vs. placebo; * for p<0.05; *** for p<0.001 (Vollenweider, Gamma, et al., 1998).*

In this study, MDMA produced high OSE[42] (oceanic boundlessness), low VUS[43] (visionary restructuralization) and low AIA[44] (dread of ego-dissolution) scores.

Cole and Sumnall (2003a) provide a comprehensive collection of all subjective positive and negative effects (self-)reported in clinical studies *and* large-scale surveys targeting recreational users (Table 1).

[42] Corresponding item clusters: “derealization”, “depersonalization”, “alterations of the sense of space and time”, “positive basic mood”, and “mania-like experience.”
[43] Corresponding item clusters: “illusions”, “hallucinations”, “synesthesias”, “changed meaning of percepts”, “facilitated recollection of memories”, and “facilitated imagination”.
[44] Corresponding item clusters: “frightening derealization”, “thought disorder”, “delusion”, “loss of thought control”, and “loss of body control”.

| Positive psychological effect | Negative psychological effect |
|---|---|
| Altered time perception | Agitation/restlessness |
| Compassion | Amnesia/vagueness |
| Confidence | Anxiety/fear |
| Cognitive changes | Blurred vision/visual distortions |
| Decreased aggression | Cognitive deficits |
| Decreased alienation | Confusion |
| Decreased defensiveness | Decreased libido |
| Decreased fear | Depersonalisation |
| Decreased impulsivity | Depression |
| Decreased obsessive/compulsive behaviour | Excessive mood swings |
| Distorted vision | Fatigue/exhaustion |
| Empathy | "Flashbacks" |
| Escape from worries | Increased aggression |
| Euphoria | Increased defensiveness |
| Exhilaration/excitement | Increased obsessiveness/ compulsiveness |
| Friendly | Insomnia/sleep disturbance |
| Hallucinations | Irritability |
| Heightened perception | Motivational deficits |
| Humour | Panic attacks |
| In touch with body | Paranoia |
| Increased energy | Passing out |
| Increased perception of colour | Vertigo/dizziness/ataxia |
| Increased perception of sound | Weight loss/decreased appetite |
| Increased perception of touch | |
| Openness | |
| Relaxation | |
| Sexual arousal | |
| Talkative | |
| Wisdom | |

*Table 1. Self-reported positive and negative psychological effects reported after ingestion of MDMA or Ecstasy tablets (Cole & Sumnall, 2003a).*

### *3.3.2 Undesired psychological and cognitive effects*

While MDMA is generally highly anxiolytic, anxiety can arise during the onset of main drug-effects. In high doses and inappropriate environments, this come-up anxiety may exacerbate into a panic attack.[45]

In clinical settings, potential undesired cognitive effects include: thought disturbances like difficulty concentrating, accelerated thinking, impaired decision making, thought blocking, or losing track of one's thoughts (Vollenweider et al., 2002). These effects are generally mild; confused or delusional thinking or paranoid ideation does not occur (ib.).

MDMA has no influence on performance in the *Stroop test* (Vollenweider, Gamma, et al., 1998) indicating that it does not impair selective attention and it increases psychomotor speed without affecting psychomotor accuracy (Dumont, Schoemaker, et al., 2009). In the study by Dumont et al. (2008), 100mg of MDMA did not significantly reduce executive function, visuospatial and visuomotor function, and immediate recall but reduced delayed recall (retrieval of verbal information) and attention – the detrimental effects on cognitive function were similar to a low dose of ethanol (2-3 drinks or 0.6‰ BAC).

Although experimental data are scarce, clinical experience shows that a therapeutic dose of MDMA does not affect cognitive or executive functions on a level that could be called 'impairing'.

While the addictive potential of MDMA has proven to be irrelevant in clinical and therapeutic use[46], the addictive potential of MDMA should be briefly outlined:

Generally "most people who use psychoactive drugs do so without experiencing any problems, but some do develop problems related to their use" (Degenhardt & Hall, 2010, p.117). This statement is also true for MDMA.

MDMA is structurally and pharmacologically related to substances (e.g., amphetamine and methamphetamine) that are strongly reinforcing and known to cause users to apply them more often than they intended, sometimes with catastrophic results. Reinforcing qualities are mainly mediated by dopaminergic action and MDMA also displays those actions –

[45] N.B.: During MDMA assisted psychotherapy sessions transient states of heightened anxiety are not necessarily undesired but may occur as a part of a successful therapeutic process.

[46] There are no documented cases of participants who started abusing MDMA after taking part in such studies.

however in animal models MDMA is significantly less reinforcing than related substances (Degenhardt & Hall, 2010). Still MDMA occasions problematic use patterns – that is escalating and compulsive use – in some recreational users. However, MDMA abuse is known to not only result in short-term physiological tolerance, in the sense that higher doses are needed to reach the desired effect, but also in an idiosyncratic psychological tolerance towards the unique and sought after effects (cf. Kirkpatrick, Baggott, et al., 2014). This tolerance cannot be compensated by higher doses; in the contrary: prolonged use and dose escalation regularly lead to increased side effects, unpleasant experiences, and dysphoric after effects. Additionally, in many users tolerance seems to be chronic and irreversible after extended abuse. Therefore MDMA use has *some* self-limiting properties and MDMA dependency can be seen as a transient phenomenon. MDMA seems to lose its appeal in many who abuse it.

In sum the addictive potential of MDMA is more similar to the *psychological* addiction sometimes seen with psychedelic substances and less similar to the clear and marked dependence to stimulants or other known addictive drugs (e.g., opioids, ethanol) (Degenhardt & Hall, 2010).

Among recreational users, MDMA has a reputation for producing unpleasant short term sequelae, often referred to as 'crash'.[47] Furthermore the depletion of serotonin after prolonged and/or high dose MDMA consumption may lead to affective disturbances mimicking (short) depressive episodes. Since these symptoms usually arise with a latency of 1-2 days, this phenomenon was coined 'suicide Tuesday' by followers of the rave scene. Most likely these symptoms occur due to overuse of MDMA, co-administration of other psychoactive substances, exhausting life style (especially circadian disturbances), and other environmental, behavioral, and psychological factors, including poor or missing psychological integration of the drug induced experience(s). As a matter of fact, these *severe* comedown, crash, or hangover phenomena have neither occurred in clinical nor in therapeutic trials. Table 2 shows the 24h sequelae of MDMA compared to placebo reported by Vollenweider, Gamma, et al. (1998). Note that these side-effects are rather somatic than psychological or affective.

[47] This phenomenon is typical for stimulant or opioid abuse.

| Subjective Sensation | Placebo Number of Subjects (Total $n = 13$) | MDMA Number of Subjects (Total $n = 13$) |
|---|---|---|
| Lack of appetite | 0 | 6 |
| Lack of energy | 1 | 6 |
| Thirst | 0 | 6 |
| Fatigue | 5 | 5 |
| Feeling of restlessness | 0 | 5 |
| Heavy legs | 0 | 5 |
| Insomnia | 0 | 5 |
| Feeling of weakness | 0 | 4 |
| Frequent urge to urinate | 1 | 4 |
| Difficulty concentrating | 1 | 4 |
| Decreased libido | 0 | 4 |
| Jaw clenching (bruxism) | 0 | 4 |
| Perspiration | 0 | 3 |
| Increased sensitivity to cold | 1 | 3 |
| Brooding | 0 | 3 |
| Private or job-related worries | 3 | 3 |
| Headache | 0 | 2 |
| Increased need to sleep | 1 | 2 |
| Forgetfulness | 0 | 1 |

*Table 2. Short-term sequelae 24h after ingestion of MDMA (Vollenweider, Gamma, et al., 1998).*

Table 3 provides an overview of the side effects reported both acutely and in the 7 days after the therapy sessions in the study by Mithoefer et al. (2011) compared to the placebo condition. All subjects in this trial were treatment-resistant PTSD patients – a population that should be particularly vulnerable to adverse psychological and affective sequelae. The authors concluded that no serious drug-related adverse effects had occurred.

| | Day of MDMA sessions (2) *N* (%) | Day of placebo sessions (2) *N* (%) | Within 7 days after MDMA sessions *N* (%) | Within 7 days after placebo session *N* (%) |
|---|---|---|---|---|
| | Subjects = 12 Sessions *N* = 24 | Subjects = 8 Sessions *N* = 16 | Subjects = 12 Sessions *N* = 24 | Subjects = 8 Sessions *N* = 16 |
| Anxiety | 14 (58%) | 13 (81%) | 13 (54%) | 7 (44%) |
| Decreased concentration | 3 (13%) | 1 (6%) | 6 (25%) | 0 |
| Derealization, detachment | 0 | 0 | 1 (4%) | 0 |
| Diarrhea | 0 | 0 | 3 (13%) | 0 |
| Dizziness | 9 (38%) | 2 (13%) | 3 (13%) | 1 (6%) |
| Drowsiness | 2 (8%) | 3 (19%) | 0 | 2 (13%) |
| Dry mouth | 4 (17%) | 1 (6%) | 1 (4%) | 0 |
| Fatigue | 11 (46%) | 8 (50%) | 18 (75%) | 12 (75%) |
| Feeling cold | 10 (42%) | 3 (19%) | 1 (4%) | 0 |
| General infection | 1 (4%) | 0 | 0 | 2 (13%) |
| Headache | 14 (58%) | 9 (56%) | 6 (25%) | 4 (25%) |
| Heavy legs | 2 (8%) | 0 | 1 (4%) | 0 |
| Impaired balance | 6 (25%) | 0 | 0 | 0 |
| Insomnia | 13 (54%) | 10 (63%) | 9 (38%) | 9 (56%) |
| Irritable | 2 (8%) | 3 (19%) | 8 (33%) | 3 (19%) |
| Loss of appetite | 8 (33%) | 1 (6%) | 9 (38%) | 0 |
| Low mood | 4 (17%) | 2 (13%) | 10 (42%) | 8 (50%) |
| Muscle tension | 4 (17%) | 2 (13%) | 2 (8%) | 1 (6%) |
| Nausea | 12 (50%) | 2 (13%) | 7 (29%) | 4 (25%) |
| Need more sleep | 0 | 1 (6%) | 5 (21%) | 2 (13%) |
| Nystagmus | 1 (4%) | 0 | 0 | 0 |
| Pain | 1(4%) | 4 (25%) | 1 (4%) | 1 (6%) |
| Panic, re-experiencing | 0 | 0 | 1 (4%) | 1 (6%) |
| Parasthesias | 2 (8%) | 0 | 0 | 0 |
| Perspiration | 4 (17%) | 1 (6%) | 0 | 1 (6%) |
| Restless | 5 (21%) | 2 (13%) | 1(4%) | 0 |
| Rumination | 1 (4%) | 1 (6%) | 3 (13%) | 2 (13%) |
| Somatic sensations | 1 (4%) | | 1 (4%) | |
| Thirst | 2 (8%) | 1 (6%) | 0 | 0 |
| Tight jaw | 19 (79%) | 3 (19%) | 6 (25%) | 2 (13%) |
| Upper GI burning | 1 (4%) | 0 | 0 | 0 |
| Upper respiratory infection | 0 | 0 | 2 (8%) | 2 (13%) |
| Visual disturbance | 1(4%) | 0 | 2 (8%) | 0 |
| Weakness | 1 (4%) | 1 (6%) | 6 (25%) | 0 |

*Table 3. Number of instances of spontaneously reported side effects (Mithoefer et al., 2011).*

### *3.3.3 Final thoughts on the MDMA phenomenology regarding its usefulness for psychotherapy:*

The trademark features of MDMA are undoubtedly that it produces powerful prosocial effects[48], a profound sense of well-being, and strong anxiolysis. However, the anxiolysis that MDMA provides is unusual: Unlike typical anxiolytic drugs – such as benzodiazepines –

[48] A feature that is necessarily dampened in laboratory settings.

MDMA does not dull feelings of anxiety but creates a sense of detachment, thereby reducing the sensation of imminent threat. More metaphorically speaking: the anxiety is still there but the core of the personality does not feel threatened by it. Anxiety – along with other threatening emotional contents – rather becomes the subject of analytic reflection than an autonomous state from which there is no perceived escape of.
MDMA thus creates an open space between the self and contents that are perceived as threatening to the self. During a psychotherapeutic process, this gives room for psychological growth – especially in persons that are surrounded and consumed by fear, as it is seen in PTSD patients for example.
Translated into psychoanalytic ductus, these effects equal that healthy parts of the ego seem to be strengthened, 'the guards of resistance are lowered'[49] and that unconscious – emotionally painful – contents can be brought to awareness and are ready for reprocessing and adaptive integration.
The defining perspective shift, that a therapeutic dose of MDMA provides, is that subjects typically attain a strong sense of loving (self-)acceptance – also and especially in face of their most painful memories, their deepest fears, and their most objectionable flaws.
An exemplary statement during such a state could be: "The world is well, I am well, and nothing can harm my integrity."

## 3.4 Physiological effects and adverse effects

Chapter 3.2 gave an overview of the subjective and psychological effects of MDMA in humans – obviously many of those effects cannot be separated from effects that are more somatic. In contrast, this chapter is concerned with terms that are interesting or critical from a decidedly medical perspective.

[49] But – in contrast to psychedelic substances – resistance is not forcefully dissolved. Ego-integrity is maintained, but defense mechanisms seem to become more of a choice than a fact.

### *3.4.1 Physiological effects*

MDMA has sympathomimetic properties. It therefore has hypertensive effects, peaking about 2h after administration. In the study by Vollenweider, Gamma, et al. (1998), increases were in the range of 10 to 30 mm Hg for systolic blood pressure and 5 to 10 mm Hg for diastolic blood pressure; pulse rates were also increased.

Similarly Lester et al. (2000) report that mean systolic blood pressure was increased by 25 mm Hg, diastolic blood pressure by 7 mm Hg, and heart rate by 28 bpm. According to Cole and Sumnall (2003a), MDMA does not reliably increase body temperature in laboratory settings. This is noteworthy since there have been fatalities due to overheating in recreational users of MDMA.[50]

Equal changes were recorded in the therapeutic trial by Mithoefer et al. (2011); elevations of blood pressure, pulse rate, and temperature were minor (Table 4) and did not result in any medical complications.

| | MDMA | | Placebo | |
|---|---|---|---|---|
| Systolic BP | Mean (St. Dev.) | Range | Mean (St. Dev). | Range |
| Baseline | 117.9 (15.0) | 97/149 | 114.2 (11.6) | 92/140 |
| Maximum | 143.1 (16.3) | 117/179 | 136.4 (18.8) | 102/176 |
| Max Change | 25.2 (13.7) | 16/50 | 22.2 (15.3) | −3/57 |
| Diastolic BP | | | | |
| Baseline | 74.6 (9.4) | 56/92 | 74.4 (8.1) | 58/89 |
| Maximum | 89.0 (9.2) | 74/113 | 88.2 (10.5) | 65/106 |
| Max Change | 14.4 (6.5) | 1/14 | 13.8 (7.5) | 2/28 |
| Pulse | | | | |
| Baseline | 74.3 (11.7) | 54/98 | 69.9 (10.9) | 5/92 |
| Maximum | 103.1 (15.9) | 67/135 | 92.1 (17.8) | 68/141 |
| Max Change | 28.8 (11.5) | −7/52 | 22.2 (13.7) | 3/57 |
| Temperature | | | | |
| Baseline | 36.6 (0.5) | 35.6/37.8 | 36.3 (0.6) | 35/37.2 |
| Maximum | 37.1 (0.3) | 36.7/37.8 | 37.1(0.4) | 36.7/37.8 |
| Max Change | 0.5 (0.4) | −0.6/1.5 | −0.7 (0.6) | −0.06/1.9 |

*Table 4. Physiological data during MDMA assisted therapy sessions (Mithoefer et al., 2011)*

[50] See chapter 3.4.2

### *3.4.2 Acute adverse physiological effects*

The majority of severe complications surrounding the use of MDMA/"ecstasy" can be ascribed to factors only prevalent with illicit use: (accidental) overdose, tainted products, unfavorable environment and/or conduct. Especially co-administration of other psychoactive substances (namely depressants and psychostimulants) is as dangerous as it is prevalent among many recreational users of MDMA (Cole & Sumnall, 2003a).

Hyperthermia[51] is a classic symptom among the MDMA fueled rave scene. At worst, hyperthermia induced by the *combination* of MDMA, non-stop dancing in hot, crowded environments[52], and dehydration results in rhabdomyolysis, multiple organ failure, and death. A long propagated remedy against hyperthermia – drinking copious amounts of water – has consequently led to casualties due to hyponatremia[53] fostered by MDMA-induced effects on water balance[54] (Campbell & Rosner, 2008). As a consequence of these findings, intake of *isotonic* drinks at regular intervals must be recommended both in recreational and therapeutic settings.

There is some evidence that subjects with low-activity *CYP2D6* and *COMT*[55] genotypes – 20-30% of the population – are especially vulnerable to both of those potentially lethal complications (Aitchison et al., 2012; De la Torre et al., 2004; Ramamoorthy et al., 2002). Populations with (potentially) increased risk for complications are persons with renal, hepatic, cerebro- or cardiovascular conditions. Although the evidence base concerning these risk factors is limited, those people should generally abstain from MDMA; in the therapeutic context screening for such conditions is imperative.

Severe or life threatening complications surrounding MDMA exposure generally require a 'perfect storm' scenario, where an unlikely combination of idiosyncratic dispositions, the pharmacology of MDMA and environmental factors synergize towards catastrophic

[51] 'Heat stroke'
[52] In animal models high ambient temperatures increase MDMA-induced hyperthermia, lethality, and neurotoxicity (Cole & Sumnall, 2003a).
[53] 'Water intoxication'
[54] MDMA and some of its metabolites release antidiuretic hormone (arginine vasopressin) and reduce $Na^+$ plasma levels.
[55] Enzymes responsible for the metabolization of MDMA

outcomes.[56] As yet, no severe complications have been recorded under controlled circumstances.

Table 5 lists all the adverse acute effects reported in the clinical study by Vollenweider, Gamma, et al. (1998) applying 1.7mg/kg PO. According to the authors, those effects were neither considered severe by the subjects nor were they unexpected.

| Subjective Sensation | Placebo Number of Subjects (Total $n = 13$) | MDMA Number of Subjects (Total $n = 13$) |
|---|---|---|
| Jaw clenching (bruxism) | 0 | 8 |
| Lack of appetite | 0 | 8 |
| Difficulty concentrating | 1 | 8 |
| Impaired balance/gain | 0 | 8 |
| Restless legs | 0 | 6 |
| Perspiration | 0 | 5 |
| Heavy legs | 0 | 5 |
| Increased sensitivity to cold | 1 | 5 |
| Thirst | 0 | 5 |
| Forgetfulness | 0 | 5 |
| Palpitations | 0 | 4 |
| Feelings of restlessness | 0 | 4 |
| Insomnia | 0 | 4 |
| Dizziness or vertigo | 0 | 4 |
| Tremor | 0 | 4 |
| Paresthesias | 0 | 4 |
| Weakness | 0 | 3 |
| Hot flashes | 1 | 3 |
| Being cold | 0 | 3 |
| Inner tension | 0 | 3 |
| Frequent urge to urinate | 1 | 2 |
| Fatigue | 5 | 1 |
| Nausea | 0 | 1 |
| Private or job-related worries | 3 | 0 |

*Table 5. Acute sequelae of MDMA (Vollenweider, Gamma, et al., 1998).*

[56] Cole and Sumnall (2003a) mention *two* recorded cases where adverse reactions could verifiably not be attributed to environmental variables.

### *3.4.3 Neurotoxicity*

MDMA is notorious for its supposed long-term neurotoxic effects and hundreds of papers have been written on that topic. In this paper the neurotoxicity of MDMA cannot be reviewed, but a brief overview on this research has to be presented. The aim is clearly to justify the conviction that MDMA applied in a therapeutic setting does not put patients in risk of long term structural and functional damage.

There is broad evidence that MDMA is harmful for neurophysiological processes (especially) involving serotonergic activity in rodents and non-human primates (cf. Carvalho et al., 2012; Mueller, Yuan, McCann, Hatzidimitriou, & Ricaurte, 2013; Ricaurte, DeLanney, Irwin, & Langston, 1988). In rats, selective toxicity at serotonergic neurons is typically induced by chronic and/or high doses; typically 20mg/kg *injected* twice daily for 4 days or 20mg/kg once daily for 10 days (cf. Mayerhofer, Kovar, & Schmidt, 2001). Modest doses and lower frequencies (4mg/kg twice weekly) produced no serotonergic damage (O'shea, Granados, Esteban, Colado, & Green, 1998). A typical therapeutic dose in humans is 125mg – that is 1.79mg/kg for a 70kg human – administered 2-4 times with several weeks between treatment sessions.

N.B.: There is an interesting homology between this research and the research on the neurotoxicity of amphetamine: This psychostimulant is a known drug of abuse and also a widely prescribed (maintenance) medication for ADHD. While regimens allegedly mimicking human abuse patterns prove neurotoxicity, paradigms resembling therapeutic regimens may even hint to adaptive effects including dendritic growth (cf. Advokat, 2007). This – rudimentarily related – example does not only highlight the fact that different research questions in the same field may lead to seemingly contradicting results but also that the explicatory power of pathogenetic, abuse-oriented paradigms is limited in salutogenetic, therapeutic contexts.

There is also some direct (cf. Benningfield & Cowan, 2013; McCann, Szabo, Scheffel, Dannals, & Ricaurte, 1998) and indirect evidence – via measurement of cognitive functions (cf. Wagner, Becker, Koester, Gouzoulis-Mayfrank, & Daumann, 2013) and psychological wellbeing (cf. Thomasius et al., 2006) – for neurotoxicity in humans involved in long term use

of the street drug “ecstasy”. Anecdotal evidence from subjects with a history of long term, high dose and/or high frequency abuse of “ecstasy” as well as health practitioners treating those subjects suggests that chronic abuse of MDMA may *cause* severe harm for at least some subjects.

While there is conclusive pre-clinical evidence that MDMA can be neurotoxic in specific circumstances[57] and while human use of “ecstasy” has been shown to be *associated* with memory related (Schilt et al., 2007; Wagner et al., 2013) functional deficits and psychiatric symptoms, it is still a matter of debate if the application of therapeutic doses of pure MDMA in controlled environments poses any significant risks for long term detrimental effects at all (Vollenweider, Gamma, Liechti, & Huber, 1999; Vollenweider et al., 2001).

Two crucial problems can be identified in the research on long-term detrimental effects of MDMA:
The first one is the problem of translation from animal models to humans, especially regarding dosages as well as the impossibility to translate complex functional deficits that may potentially occur in humans. The translational problems surrounding the pharmacological issue of toxicity and safety of MDMA has sparked tough academic debates (cf. Lieberman & Aghajanian, 1999; McCann & Ricaurte, 2001; Vollenweider et al., 1999; Vollenweider et al., 2001). Additionally, the use of psychoactive substances inevitably confronts researchers with questions of a more philosophical nature that cannot be approached via animal models in principle as higher consciousness or at least the ability to communicate sentiences is lacking (cf. Shulgin & Nichols, 1978).
However, in regard to the most frequently used animal model, Green, King, Shortall, and Fone (2012) conclude that:

> Taking into account the differences in the pharmacokinetic profile of MDMA in rats and humans, […] doses currently being used to investigate the possible therapeutic benefits of the drug are unlikely to produce any severe acute or importantly any long-

[57] However, proof of acute neurotoxic effects does not mean that those effects are permanent (Mayerhofer et al., 2001) and necessarily result in long term functional deficits. According to Cole and Sumnall (2003a) in animal models neurotoxic effects are not manifested behaviorally, despite detectable neurochemical changes.

> term neurotoxic damage in the human brain, particularly if given as a single acute administration in the absence of other agents in a therapeutic milieu. (p.1533)

The last part of this statement also hints to the second problem: the low methodological quality in the greatest part of studies concerned with detrimental effects of “ecstasy” consumption. In most cases, users of “ecstasy” are (retrospectively) compared to non-users – of course such studies are neither randomized nor placebo controlled. They are obviously subject to sampling effects.

And moreover:

- The street drug “ecstasy” is not MDMA (see chapter 2.2.1),
- there is no control of doses, frequency, and circumstances of use (hydration and ambient temperature are especially important),
- no control of use of other psychoactive substances or detrimental life-style factors (e.g., sleep behavior, nutrition) often seen in users of psychoactive substances (cf. Cole & Sumnall, 2003a),
- pre-existing confounders may mediate both increased drug use and physiological or neurocognitive differences (Krebs & Johansen, 2012).

Publications disregarding those factors are obviously impractical in an attempt to judge the risks and potentials of MDMA application in a controlled clinical setting.

Those limitations call either at least for prospective longitudinal studies with the exclusion of as many potentially confounding factors as possible or at best the experimental method. The former has been achieved in a naturalistic, yet meticulously controlled study by Halpern et al. (2011) that failed to demonstrate marked residual cognitive effects in “ecstasy” users. Similarly a few methodologically advanced retrospective studies (Bedi & Redman, 2008; Hanson & Luciana, 2010; Hoshi et al., 2007; Roiser, Rogers, & Sahakian, 2007) on recreational use report either negative findings or clinically insignificant differences between users and non-users. The fact that the high prevalence of uncontrolled “ecstasy” use has left no significant impact on the public health scale emphasizes these findings (Cole & Sumnall, 2003a; Doblin et al., 2014).

While these findings are interesting, their scope limits their validity regarding the safety of MDMA assisted psychotherapy. The best source of evidence are certainly the controlled clinical trials applying MDMA that have been finished by now. Doblin et al. (2014) determine that “more than 850 participants have participated in regulatory-approved MDMA research without reporting any persisting drug-related harm” (p.107). Potential long term adverse neuropsychological effects were assessed in detail during the therapy trial by Mithoefer et al. (2011) and Mithoefer et al. (2013); no evidence for neurocognitive decline was found.

Despite this growing evidence for the absence of neurodegenerative sequelae and the favorable risk-benefit ratio of MDMA in a psychotherapeutic setting, the topic is still regarded as highly controversial by a minority of researchers: The review by Parrott (2013) is exemplary; however this paper was thoroughly rebutted by Doblin et al. (2014).[58]

### *3.4.4 Interactions of a therapeutic application of MDMA with other pharmacological interventions*

There are two possibilities for dangerous effects when MDMA and other pharmaceuticals are co-administered: competitive metabolism and psychopharmacological interactions.

Drugs that are metabolized by the same enzyme as MDMA – CYP2D6 – are contraindicated. This includes antiretroviral drugs such as ritonavir (a HIV-drug) and OTC-medications such as dextromethorphan.
The combination of MDMA and MAO inhibitors may cause serotonin syndrome and is potentially lethal. Some MAO inhibitors are used as psychiatric medications (e.g., moclobemide) and must not be combined with any drugs that increase monoamine concentrations, including MDMA. Antiretroviral drugs and MAO inhibitors are the main cause of life threatening interactions with MDMA (De la Torre et al., 2004).

[58] See chapter 2.2.3

The classes of SSRIs, SNRIs, and antipsychotics are contraindicated too; while these combinations are not (necessarily) dangerous, those substances block the binding sites of MDMA and inhibit the effects (Hysek, Simmler, et al., 2012; Liechti & Vollenweider, 2001). The indications for antipsychotic drugs contradict MDMA assisted psychotherapy anyway but SSRIs/SSRIs are still commonly prescribed for PTSD patients and need to be tapered off completely before any therapeutic application of MDMA.
Although there is no direct empirical evidence, it can be assumed that *all* psychoactive substances that act on or interact with the same neurotransmitter systems as MDMA should be avoided – this includes practically all psychiatric drugs.[59]

Sedatives, such as benzodiazepines, do not interact with MDMA on a psychopharmacological level but contradict the psychological rationale of MDMA assisted psychotherapy as well as exposure based trauma therapies in general.

## 3.5 Experimental psychology

MDMA is known for its unique prosocial features: Increased empathy and sociability are universally ascribed to the spectrum of its effects in recreational and clinical settings. Those effects are presumably linked to MDMA induced oxytocin release (Dumont, Sweep, et al., 2009). Scientific inquiry of this effect has focused on objective measurement of cognitive[60] and emotional[61] empathy as well as social behavior.

Regarding the effects of MDMA on 'mind reading'-tasks[62], the results show consistently that MDMA increases self-reported empathogenic feelings (sociability, friendliness, openness…) but that it does not improve *cognitive* empathy overall; instead the ability to identify emotional cues depends on their valence:

[59] Apart from pregabalin and gabapentin, which only have gabaergic action and are renally excreted.
[60] The ability to recognize emotional states in others.
[61] The emotional response to another person's emotional state
[62] Recognition of emotional states.

The ability to identify negative or threat related stimuli (fearful, angry, sad expressions) is reduced and the ability to identify positive socio-emotional stimuli (happy, friendly expressions) is increased (Baggott et al., 2010; Bedi et al., 2010; Hysek, Domes, et al., 2012; Hysek et al., 2014; Kirkpatrick, Lee, Wardle, Jacob, & de Wit, 2014). In contrast, *emotional* empathy is increased by MDMA as shown by Hysek et al. (2014). In the same study, prosocial behavior was significantly increased in men but not in women.

Altogether these results show that MDMA enhances the emotional response to other persons' emotional states and alters the ability to recognize emotional states in others: specifically it lowers the reactivity to *negative* social stimuli and enhances reactivity to *positive* social stimuli. In general, MDMA increases the value of social contact and closeness and creates a *positive emotional bias* that is specific to social situations (Wardle, Kirkpatrick, & de Wit, 2014). It reduces the perception, impact, and – possibly – consequences of negative socio-emotional contents. These results are underpinned by the finding that MDMA decreases the perception of rejection (corresponds to social threat) in a simulated social situation (Frye, Wardle, Norman, & de Wit, 2014). However, more naturalistic experimentation is needed to investigate effects on social behavior.

The efficacy of MDMA as a psychotherapeutic adjunct may be partly explained by those unusual prosocial effects and their implications for the therapeutic alliance.

## 3.6 Neuroimaging

Functional imaging studies exploring the acute effects of MDMA are rare. Until now, only two studies have been conducted to study the effects on spontaneous brain activity and only one each addressed prosocial effects and therapeutic application.

In the steady state PET study by Gamma et al. (2000), MDMA increased brain function in the ventromedial frontal and occipital cortex, inferior temporal lobe and cerebellum, and decreased activity in the motor and somatosensory cortex, temporal lobe including left

amygdala, cingulate cortex, insula, and thalamus – decrease in the (left) amygdala is thought to be the neural substrate of MDMA-induced mood enhancement.
Carhart-Harris, Kevin, et al. (2014)[63] found reductions of spontaneous cerebral blood flow (CBF) in the visual cortex, thalamus, somatosensory cortex, right hippocampus, and right amygdala. The intensity of subjective effects was positively correlated with decrease in the right amygdala and right hippocampus. In this study, there were no significant increases in CBF in any region. Interestingly, increase in amygdala-hippocampal Resting-state Functional Connectivity (RSFC) was observed[64] – this is an inversion of decreased amygdala-hippocampal RSFC seen in PTSD patients, which may relate to the impaired ability to contextualize affective information. Likewise mPFC-hippocampal-RSFC was also decreased; increase of this RSFC is a marker for anxiety states.

The alterations in the perception of socio-emotional cues described in chapter 3.5 are backed by the finding that MDMA attenuates left amygdala response to angry expressions and enhances ventral striatum response to happy expressions (Bedi, Phan, Angstadt, & de Wit, 2009). Amygdala activity is naturally increased by threat-related social signals and the ventral striatum is central for reward processing, including rewarding social stimuli. Both effects may help explain increased social approach behavior and sociability as well as potential improvements of therapeutic relationships.

Carhart-Harris et al. (2013) directly targeted psychotherapeutic application: Subjects were confronted with personalized cues of their favorite and worst autobiographical memories. The positive emotional bias of MDMA (in this trial a dose of 100mg) was replicated and generalized on stored memories: Favorite memories were rated as significantly more vivid, emotionally intense, and positive, worst memories were rated as less negative. The authors also report two informative qualitative comments on this effect:
"'The bad memories were less salient [under MDMA] and I thought about them in a matter of fact way.' And another: 'When I reached back for the bad memories [under MDMA] they did not seem as bad; In fact, I saw them as fatalistic necessities for the occurrence of later good events'" (Carhart-Harris et al., 2013, p.6).

[63] This and the following studies applied fMRI.
[64] Correlations between this effect and the intensity and positive mood effects of MDMA were also found but those were only near significant.

Additionally, an increase in activations to favorite memories in the ventral visual and somatosensory cortices after MDMA was observed. This indicates the intensification of memory vividness. Significantly reduced activations to worst memories were observed in the left anterior temporal cortex.[65] Amygdala reactivity was not altered; however this could be explained by the fact that healthy subjects – in contrast to PTSD patients – do not feel actually threatened by negative memories.

Up to now all experimental or functional imaging studies have been conducted with healthy subjects. Studying the perception, the behavioral, and neural response to trauma cues in PTSD patients under the influence of MDMA will be a further route of investigation to understand the therapeutic efficacy of MDMA.[66]

[65] An area involved in processing negative emotions and densely connected with the amygdala.
[66] Such studies are currently being planned (Ben Sessa, personal communication, December 9, 2014).

# 4. Posttraumatic stress disorder (PTSD)

This chapter will provide a concise exposition of posttraumatic stress disorder.
In a nutshell PTSD is a severe and disabling condition associated with high levels of suffering and loss of functionality. PTSD is often simplistically described as a 'normal reaction to an abnormal event', this means that the pathology can – unlike all other major mental disorders – be causally linked to the exposure to one or multiple external (*traumatic*) events. The condition often chronifies and aggravates, suicide risk is increased. This is especially tragic as in a significant proportion of patients the condition remains resistant to current treatment approaches.

## 4.1 Diagnosis, epidemiology, etiology, and pathology

### *4.1.1 Diagnosis*

Table 6 is an extract from the *Diagnostic and Statistical Manual of Mental Disorders: DSM-5* (American Psychiatric Association, 2013, p.271 ff.).

| Diagnostic Criteria for Posttraumatic Stress Disorder (DSM-V 309.81) | |
|---|---|
| Note: The following criteria apply to adults, adolescents, and children older than 6 years. | |
| A. Exposure to actual or threatened death, serious injury, or sexual violence in one (or more) of the following ways: | 1. Directly experiencing the traumatic event(s).<br>2. Witnessing, in person, the event(s) as it occurred to others.<br>3. Learning that the traumatic event(s) occurred to a close family member or close friend. In cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental.<br>4. Experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g., first responders collecting human remains: police officers repeatedly exposed to details of child abuse).<br>Note: Criterion A4 does not apply to exposure through electronic media, television, movies, or pictures, unless this exposure is work related. |
| B. Presence of one (or more) of the following intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred: | 1. Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s).<br>2. Recurrent distressing dreams in which the content and/or affect of the dream are related to the traumatic event(s).<br>Note: In children, there may be frightening dreams without recognizable content.<br>3. Dissociative reactions (e.g., flashbacks) in which the individual feels or acts as if the traumatic event(s) were recurring. (Such reactions may occur on a continuum, with the most extreme expression being a complete loss of awareness of present surroundings.)<br>4. Intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).<br>5. Marked physiological reactions to internal or external cues that symbolize or resemble an aspect of the traumatic event(s). |
| C. Persistent avoidance of stimuli associated with the traumatic event(s), beginning after the traumatic event(s) occurred, as evidenced by one or both of the following: | 1. Avoidance of or efforts to avoid distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).<br>2. Avoidance of or efforts to avoid external reminders (people, places, conversations, activities, objects, situations) that arouse distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s). |
| D. Negative alterations in cognitions and mood associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following: | 1. Inability to remember an important aspect of the traumatic event(s) (typically due to dissociative amnesia and not to other factors such as head injury, alcohol, or drugs).<br>2. Persistent and exaggerated negative beliefs or expectations about oneself, others, or the world (e.g., "I am bad," "No one can be trusted," 'The world is completely dangerous," "My whole nervous system is permanently ruined").<br>3. Persistent, distorted cognitions about the cause or consequences of the traumatic event(s) that lead the individual to blame himself/herself or others.<br>4. Persistent negative emotional state (e.g., fear, horror, anger, guilt, or shame).<br>5. Markedly diminished interest or participation in significant activities.<br>6. Feelings of detachment or estrangement from others.<br>7. Persistent inability to experience positive emotions (e.g., inability to experience happiness, satisfaction, or loving feelings). |
| E. Marked alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following: | 1. Irritable behavior and angry outbursts (with little or no provocation) typically expressed as verbal or physical aggression toward people or objects.<br>2. Reckless or self-destructive behavior.<br>3. Hypervigilance.<br>4. Exaggerated startle response.<br>5. Problems with concentration.<br>6. Sleep disturbance (e.g., difficulty falling or staying asleep or restless sleep). |
| F. Duration of the disturbance (Criteria B, C, D, and E) is more than 1 month. | |
| G. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning. | |
| H. The disturbance is not attributable to the physiological effects of a substance (e.g., medication, alcohol) or another medical condition. | |
| Specify whether:<br>With dissociative symptoms: The individual's symptoms meet the criteria for posttraumatic stress disorder, and in addition, in response to the stressor, the individual experiences persistent or recurrent symptoms of either of the following: | 1. Depersonalization: Persistent or recurrent experiences of feeling detached from, and as if one were an outside observer of, one's mental processes or body (e.g., feeling as though one were in a dream; feeling a sense of unreality of self or body or of time moving slowly).<br>2. Derealization: Persistent or recurrent experiences of unreality of surroundings (e.g., the world around the individual is experienced as unreal, dreamlike, distant, or distorted).<br>Note: To use this subtype, the dissociative symptoms must not be attributable to the physiological effects of a substance (e.g., blackouts, behavior during alcohol intoxication) or another medical condition (e.g., complex partial seizures). |
| Specify if:<br>With delayed expression: If the full diagnostic criteria are not met until at least 6 months after the event (although the onset and expression of some symptoms may be immediate). | |

*Table 6. Diagnostic Criteria for Posttraumatic Stress Disorder (American Psychiatric Association, 2013)*

The DSM provides the most common framework not only for the diagnosis of PTSD but also for (long term) clinical outcomes measurement. The derived psychodiagnostic tool is the *Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)* (Weathers et al., 2013).
Other tools typically used to assess PTSD symptoms in clinical studies applying MDMA in the therapy of PTSD are the *Impact of Events Scale-Revised (IES-R)* (Christianson & Marren, 2008) and the *Posttraumatic Diagnostic Scale* (Foa, Cashman, Jaycox, & Perry, 1997), the more global scales *Symptom Checklist 90-Revised (SCL-90-R)* (Derogatis & Unger, 2010) as well as the *Structured Clinical Interview for Axis I Diagnosis (SCID)* (First, Spitzer, Gibbon, & Williams, 1995), and the *SCID II* for personality disorder (Gibbon, Spitzer, & First, 1997).

### *4.1.2 Epidemiology*

The lifetime prevalence of traumatic life events is approximately 80% in the U.S. and Canada and 20%-30% in Germany and Switzerland according to Breslau (2009); 50%-90% globally according to Wittchen, Gloster, Beesdo, Schönfeld, and Perkonigg (2009). The 12 months prevalence of PTSD is about 3,5% in the U.S. and 0.5%-1% in other countries according to the American Psychiatric Association (2013); 2%-5% in European countries according to Wittchen et al. (2009). The epidemiology is apparently heavily dependent on cultural factors (Wittchen et al., 2009) and is therefore a complex and controversial topic with (socio-)political implications (cf. Friedman, Resick, & Keane, 2007). Aggravatingly, since the disorder was incorporated into the DSM-III in 1980, the diagnostic criteria for PTSD have been broadened and differentiated, inevitably confounding diagnostics and epidemiology – yet rates of diagnosis have significantly increased (Wittchen et al., 2009). However, it is undisputed that only a small proportion – less than 10% according to Breslau (2009) – of trauma victims develop PTSD.
The prevalence of traumatic life events as well as PTSD in women is around twice as high as it is in men (Wittchen et al., 2009). Persons whose profession puts them in an increased risk of traumatic exposure (e.g., soldiers, police men, emergency medical personnel) also have higher rates of PTSD (American Psychiatric Association, 2013).

The DSM-5 estimates the lifetime risk for PTSD in the United States at 8.7%, Wittchen et al. (2009) mention 5%-10% globally, Flatten et al. (2011) 1.5%-2% for Germany.

### *4.1.3 Etiology*

The core feature of PTSD is that the etiology is always linked to (a) traumatic event(s). Those event(s) can be accidental or interpersonal, long- or short-lasting, with persons suffering long-lasting interpersonal traumatic events – such as child-abuse or war[67] – having the highest risk (50%-65%) to develop PTSD.
The exposure to (a) traumatic event(s) is *necessary but not sufficient* for the development of PTSD symptoms. Pretraumatic (e.g., early traumata, age, education), peritraumatic (e.g., duration and severity of trauma, initial reaction, sense of autonomy), and posttraumatic (e.g., social interactions/acceptance, coping strategies) risk and protective factors play a crucial role in the development of the disorder (Margraf & Schneider, 2009; Wittchen & Hoyer, 2011).

The onset of the disorder can be acute or delayed, sometimes months or even years pass between the traumatic event and expression of PTSD symptoms; however there is evidence that delayed expression is scarce: in the study by Bryant and Harvey (2002) the rate was at around 5%. Delayed expression of PTSD symptoms is commonly triggered by retraumatizing experiences or non-trauma related stressful life-events.
The majority of PTSD patients have a chronic course of symptoms with few spontaneous remissions, even after many years (Flatten et al., 2011; Wittchen et al., 2009).

[67] War is the ideal breeding ground for PTSD: Symptoms known as 'war neurosis' or 'shell shock' seen in World War I soldiers after combat related trauma were actually the first clinical depiction of PTSD. Pictures of soldiers displaying the 'thousand-yard stare' – indicating posttraumatic dissociation – became iconic during various conflicts down to the present day. In the early stages of PTSD research in the 1980s, diagnosis of the disorder was still largely reserved for male combat veterans (Wittchen et al., 2009).

There are various explanatory theories about the etiology of PTSD:

Behavioristic approaches emphasize the role of classical conditioning in the formation and operant conditioning in the maintenance of the disorder; while these approaches have severe limitations (naturally they disregard cognitions), they are still useful in animal models and in the formulation of biopsychological models of PTSD and its treatment. As the biopsychological model of PTSD is exceptionally important for MDMA assisted treatment, chapter 4.2 highlights that topic specifically.

Contemporary cognitive-behavioral theories focus on the inadequate *emotional processing* (Foa, Huppert, & Cahill, 2006; Foa & Rothbaum, 2001; Rauch & Foa, 2006) of the traumatic event that results in a *pathological fear structure*; such a pathological fear structure "contains associations among the stimulus, response, and meaning representations that distort reality and includes excessive response elements" (Foa et al., 2006, p.5).[68] As a result, essentially safe or neutral situations are associated with the trauma – that is: danger – and therefore provoke a fear response. In persons with a pathological fear structure, this process is self-perpetuating: more and more stimuli get associated with a danger meaning, resulting in a copious amount of fear provoking stimuli. Subsequently, cognitive biases and behavioral avoidance "interfere with the acquisition of relevant information that is inconsistent with the existing elements of the pathological fear structure, a process that […] constitutes the essence of recovery or emotional processing."(ib.) The result is the typical PTSD symptomatology.

The model of Ehlers and Clark (2000) provides a more cognitive perspective on chronic PTSD (see Figure 5). In this model, excessive and automatic negative appraisal of the trauma together with poor elaboration and contextualization, strong associative memory and perceptual priming lead to a constant sense of serious, current threat. Dysfunctional behavioral and cognitive strategies inhibit reappraisal and successful emotional processing.

[68] An adaptive fear structure could include a gun as stimulus, running away, hiding, and heart racing as a response and the meaning element "I am going to die".

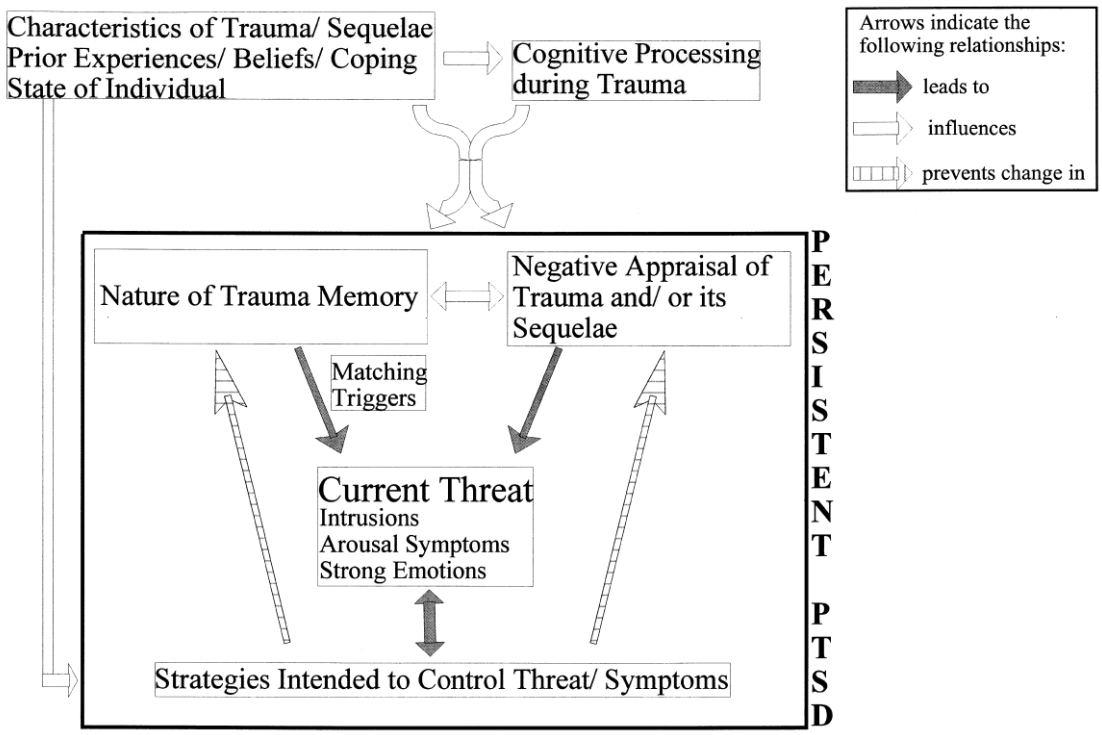


*Figure 5. A cognitive model of PTSD (Ehlers & Clark, 2000).*

In this model, the unique nature of the trauma memory is crucial for the understanding of the disorder: it makes it impossible to see the trauma as something aversive that lies in the past; instead it is seen as something that has current and ongoing negative consequences. During intrusive episodes, PTSD sufferers experience the trauma not as a memory but as something that happens 'here and now'.

### *4.1.4 Pathology*

According to the DSM-5 (American Psychiatric Association, 2013) there is a close relationship between PTSD and anxiety disorders, obsessive-compulsive, and dissociative disorders.

As already mentioned, the distinctive symptoms of PTSD are intrusions and flashbacks, where the patients may completely lose spatial and temporal orientation and (re)experience

the trauma not as a memory but as the current reality.[69] At the same time traumatic memories are often inaccessible to intentional recollection (dissociative amnesia) and are blocked by paralyzing fear, accompanied by physiological fight-or-flight-type responses. Trauma associated stimuli evoke severe distress and are therefore avoided. PTSD patients feel that they constantly 'think&talk about the trauma', when in fact they act *around* the trauma. Measures to control, suppress, and eliminate – to avoid – the trauma are adaptive from an internal perspective but consistently make matters worse. The phenomenon of emotional numbing is closely related to the symptom of avoidance: experiencing any vivid emotion goes along with the risk of triggering overwhelming flashbacks. Avoidance is both a major clinical symptom and the decisive factor that maintains PTSD symptomatology. Accordingly, PTSD patients often chose to live in isolation.
Negative emotional states and cognitive distortions go along with heightened levels of arousal and reactivity, resulting in symptoms like aggressiveness, hypervigilance, and sleep disturbances.

Comorbidities are the rule rather than the exception with PTSD patients: the DSM-5 (American Psychiatric Association, 2013) states that persons with PTSD are 80% more likely to meet diagnostic criteria for at least one other mental disorder, such as depressive, bipolar, anxiety, or substance use disorders. Around one third of PTSD patients have a primary pretraumatic disorder putting them at a higher risk of developing PTSD; in two thirds one or more comorbidities develop posttraumatically; this includes almost all other mental disorders (Wittchen & Hoyer, 2011). Suicidality is prevalent in the majority of patients and suicide risk is elevated (Gradus et al., 2010; Tarrier & Gregg, 2004).

[69] In this context, PTSD can be called a "memory disorder" (cf. Wittchen & Hoyer, 2011, p.988).

## 4.2 Neurophysiological correlates and pathophysiology

The biological correlates of PTSD are relatively well understood. For pragmatic reasons this chapter will focus on neurofunctional correlates.

PTSD is a – rapidly – *acquired* mental disorder. This means that learning processes, (fear) conditioning/extinction, memory, and associated brain structures are bound to play a significant role; namely the hippocampus (associated with memory consolidation and contextualisation), the ventromedial prefrontal cortex (vmPFC) (associated with processing risk , fear, and the inhibition of emotional responses), the dorsal anterior cingulate cortex (dACC) (associated with decision making, evaluation, and learning), and the amygdala (associated with emotional – especially fear related – learning, memory, and reactions).

The review article by Pitman et al. (2012) provides an extensive overview regarding the structural and functional neurophysiological characteristics in PTSD patients:

A reduction in the volume of the hippocampus is a structural feature in PTSD patients – however it is unclear if this is a result of trauma exposure or a pretraumatic risk factor. Likewise volume reductions in the (rostral) vmPFC and the dAAC have been found; those changes represent an acquired feature of PTSD and not a risk factor.
The amygdala is a key structure for both the recognition of dangerous stimuli and the coordination of the fear response. Its activity is modulated by higher cortical structures, namely the dACC and the vmPFC. In functional neuroimaging studies, PTSD patients show greater amygdala activation to trauma related as well as to generic emotional stimuli and also during the acquisition of conditioned fear – this amygdala reactivity is positively correlated with PTSD symptom severity. Similarly the dACC and the insular cortex, that both modulate (in this case enhance) the amygdala's expression of fear, are also hyper-reactive in PTSD patients.
The vmPFC on the other hand shows decreased activation to trauma-related or unrelated stimuli in PTSD patients and PTSD symptom severity correlates negatively with vmPFC activation during the recollection of personal traumatic events. Successful psychotherapeutic interventions increase vmPFC activation.

If these findings are taken together a neurocircuitry model of PTSD can be established (Liberzon & Sripada, 2007; Patel, Spreng, Shin, & Girard, 2012; Pitman et al., 2012):

1. Trauma exposure leads to a hyper-responsivity of the amygdala; hyperarousal and vigilance ensue.
2. Top-down control by the vmPFC is inadequate.
3. Contextualization fails[70]; amygdala hyper-responsivity is maintained, leading to attentional bias towards threat, increased fear response (hyperactivity of the dACC further promotes fear expression), impaired extinction of traumatic memories, and deficits in emotion regulation.

While this model manages to explain symptoms related to the processing of (threat-related) stimuli, it leaves other core phenomena of PTSD – namely intrusive memories – aside.
In reference to the notion of PTSD as a memory disorder, traumatic memories are not fully consolidated in the hippocampus but are 'stuck' and processed akin to current incoming stimuli – on the other hand current stimuli are not processed in a safe or neutral context but in the context of the trauma. Traumatic memories are out of context and extinction of the (ongoing) maladaptive fear response those memories are entangled with, is blocked.
It is noteworthy that this mechanism also blocks cognitive (re)appraisal – and consolidation – as higher (prefrontal) cortical structures are bypassed in face of the 'current' threat[71] and high levels of stress – as proposed by the neurocircuitry model, the automatic amygdala response takes over and thus the behavior and experience of a PTSD patient are largely dictated by a primal fight-or-flight-mode.

[70] "Cues resembling trauma are not perceived in the current context but rather independent of it — as if trauma is the actual context."(Liberzon & Sripada, 2007, p.164)
[71] A sense of current threat is also crucial in the cognitive model of PTSD by Ehlers and Clark (2000).

## 4.3 Treatment approaches for PTSD

Today it is generally acknowledged that the distinct pathology of PTSD requires specifically tailored interventions. Various psychotherapeutic methods were developed to treat the disorder, the most renowned ones are different forms of trauma-focused cognitive-behavioral psychotherapy (TFCBT) and Eye Movement Desensitisation and Reprocessing (EMDR). Psychopharmacological treatment attempts generally show limited efficacy.

### *4.3.1 Pharmacotherapy*

According to Hoskins et al. (2015) selective serotonin reuptake inhibitors (SSRIs) display small effect sizes (standardized mean difference -0.23, 95% CI -0.33 to -0.12 versus placebo) as a class in reducing PTSD symptoms. However, membership of the class does not confer efficacy equally, as drugs such as citalopram do not demonstrate efficacy. For individual agents with more than one study, there is small statistically significant evidence for the SSRIs fluoxetine, paroxetine, and sertraline and the serotonin noradrenaline reuptake inhibitor (SNRI) venlafaxine in reducing PTSD symptom severity.

Given these low effects sizes, psychopharmacological agents are second-line treatment options and should only be used if psychological interventions don't work or are not available (World Health Organization, 2013). Interestingly, PTSD patients regularly show marked reactions to placebo – in some studies greater than 40% symptom reduction (Hoskins et al., 2015). Exclusive pharmacotherapy is generally contraindicated. Especially treatment with anxiolytic psychoactive drugs – such as benzodiazepines – is critical not only due to lack of efficacy but also due to heightened addictive tendencies in PTSD sufferers (Flatten et al., 2011).

It is noteworthy that pharmacological interventions have not only been tested in the treatment but also in the secondary prevention of PTSD; that is: directly after trauma

exposure to prevent over-consolidation of traumatic memories and associated fear conditioning. The β-adrenergic blocker propranolol, glucocorticoid activation via hydrocortisone, the analgesic morphine, and the dissociative anesthetic ketamine have been proposed. However, existing data are inconclusive (Kearns, Ressler, Zatzick, & Rothbaum, 2012).

### *4.3.2 Psychotherapy*

Trauma-focussed cognitive-behavioural therapy (TFCBT) or eye movement desensitisation and reprocessing (EMDR) should be the first line treatment for PTSD (Bisson et al., 2007; Ehlers et al., 2010). Both treatments specifically address traumatic memories and the personal meanings of the event and its consequences. TFCBT and EMDR are typically delivered in outpatient settings over a course of 8-12 sessions. According to Bisson et al. (2007), both treatments have large effect sizes: versus waiting list TFCBT has a standard mean difference of -1.40 (95% CI -1.89 to -0.91) and EMDR -1.51 (95% CI -1.87 to -1.15).

Treatments that do not explicitly focus on the processing of traumatic contents – such as stress management and psychodynamic therapies – are less effective. Approaches (cognitive behavioral or psychodynamic) that are not specifically designed for the therapy of PTSD are – just as exclusive pharmacotherapy – generally regarded as obsolete (cf. Flatten et al., 2011).

While exposure to the traumatic memories is crucial for the efficacy of those treatments, the associated pain, anxiety, and – often – shame pose a severe obstacle for some patients:
The negative feelings that accompany recollection of the traumatic memories can be so overwhelming that therapeutic interventions that focus on confronting those contents are precluded.
Besides psychological resistance to therapeutic interventions, actual withdrawal from the treatment is also a serious problem in PTSD therapy: Although tolerability can be increased

with a focus on the therapeutic relationship, withdrawal rates are still as high as 30% (Bisson et al., 2007).

While this paper cannot provide detailed insights into therapeutic methods and processes, a few core principles of evidence based treatments can be pointed out:
As already mentioned, all evidence based treatments rely on confrontation and (re)processing of traumatic contents – obviously this requires a therapeutic setting that is first and foremost safe and protective. A firm therapeutic alliance and established rapport is a must, independently of specific trauma-focused therapeutic techniques. The same goes for psychoeducation[72] and relaxation techniques. Usually the trauma – and subsequent triggers and reactions – is explored before any confrontation takes place. Trauma confrontation is usually directive.

The following paragraphs outline selected treatment options with either a strong evidence base or significant potential – especially in regard to the implementation of MDMA as an adjunct:

*TFCBT*

*Prolonged exposure* (PE) is the most widely studied version of TFCBT. It is based on the emotional processing theory (Foa et al., 2006) (see chapter 4.1.3). At the base of this theory is the notion that PTSD patients possess a pathological fear structure that is activated by essentially neutral environmental stimuli and involves an excessive response as well as meaning elements that distort reality:

> For example, a survivor of a motor vehicle accident may accurately associate driving fast with danger, but also associate blue cars with danger since the car that hit him was blue. However, in reality blue cars are not more dangerous than red cars. (Rauch & Foa, 2006, p.61)

[72] The basic aim is to convey the patient that avoidance maintains symptoms and confrontation reduces symptoms.

According to Rauch and Foa (2006), the two underlying basic dysfunctional cognitions are: *The world is completely dangerous* and *one's self is totally incompetent*.
Chronic PTSD develops and is maintained because systematic avoidance hinders the disconfirmation of those convictions. Therefore effective intervention requires that the fear structure is activated and that information incompatible with the elements of the fear structure must be presented and integrated into the fear structure to replace pathological elements with realistic ones. In the therapeutic process, fear structures are activated by imaginal exposure (traumatic memories) and in vivo exposure (trauma related situations). An optimal level of activation is crucial for the treatment to be effective:

- If activation is insufficient (underengagement), the necessary modifications cannot occur. In practice, the patient may recount traumatic contents but remain detached and emotionally unengaged or numbed[73]; the contents that are actually perceived as the most threatening and meaningful are still avoided, levels of distress are *too low*.[74]
- If activation is too high (overengagement), modification of the fear structure is also prevented: overengagement often involves an overwhelming fear response, perceived loss of control, vivid flashbacks, and/or dissociation. Naturally these states prevent the processing of new and disconfirming information.

Successful exposure entails habituation to fear provoking trauma-associated stimuli and extinction of avoidance behaviors. Patients regain control over negative affects and dysfunctional cognitions are altered – which in turn reduces avoidance behavior even more.

Prolonged exposure contains both emotional and cognitive elements but focuses on emotional processing and learning theory. Exposure and extinction are the core elements of the approach. In contrast, the model by Ehlers and Clark (2000) specifically addresses cognitive elements (see chapter 4.1.3): excessive and automatic negative appraisal of the trauma, poor elaboration and contextualization as well as the unique features of the trauma memory – the perception that the trauma and threat emanating from the trauma is ongoing and imminent.

[73] Detachment and emotional numbing can be seen as a form of avoidance behavior.
[74] N.B.: Exposure based therapies regularly ask patients for their Subjective Units of Distress (SUDs) – on a scale from 0 to 100 – as a measure for emotional engagement in distressing contents.

*Cognitive processing* therapy thereby operates by 'putting the trauma in the past'. Ehlers and Clark (2000) mention three key targets for change:

- The trauma memory needs to be elaborated and integrated into the context of the individual's preceding and subsequent experience in order to reduce intrusive reexperiencing.
- Problematic appraisals of the trauma and/or its sequelae that maintain the sense of current threat need to be modified.
- Dysfunctional behavioral and cognitive strategies that prevent memory elaboration, exacerbate symptoms or hinder reassessment of problematic appraisals need to be dropped. (p.335)

The model is complementary – particularly by applying active cognitive interventions – to the emotional processing model and derived intervention strategies.

*EMDR*

EMDR uses cognitive and confrontative methods in conjunction with controlled saccadic eye movements or other external bilateral stimuli (Shapiro, 1996; Wittchen & Hoyer, 2011). Presumably the stimuli serve the purpose of distraction, facilitate an associative process, decrease avoidance, and ease trauma confrontation. However, it is unclear if the eye movements are an inherently necessary component. The basic mechanism of action is also exposure, which makes the essence of the treatment similar to TFCBT (Seidler & Wagner, 2006).

Interestingly, the eye movements serve a similar purpose as MDMA in that they improve accessibility of traumatic contents, however EMDR lacks the improvement of the therapeutic alliance that MDMA presumably entails.

*CBCT*

A novel treatment option, putting special focus on the interpersonal aspects of the pathology of and recovery from PTSD, is Cognitive-Behavioral Conjoint Therapy (CBCT). The treatment fosters a more naturalistic approach as well as benefits of social support by incorporating a significant other in the therapeutic process. CBCT also acts on threat that PTSD poses to long-term relationships. Existing results are promising (Monson et al., 2012). CBCT is specifically mentioned here because – presumably – a treatment approach in a conjoint setting is particularly suitable for the implementation of MDMA-assisted treatment sessions. In the very first paper on the clinical effects of MDMA, Greer and Tolbert (1986) already state:

> In general, it is reasonable to conclude that the single best use of MDMA is to facilitate more direct communication between people involved in a significant relationship. Not only is communication enhanced during the session, but afterward as well. Once a therapeutically motivated person has experienced the lack of true risk involved in direct and open communication, it can be practiced without the assistance of MDMA. This ability can not only help resolve existing conflicts but can also prevent future ones from occurring due to unexpressed fears or misunderstandings. Regardless of the mechanism, most subjects expressed a greater ease in relating to their partners, friends, and co-workers for days to months after their sessions. (p.326)

It is conceivable that there might be significant synergistic effects when the pro-social facilitator, that is MDMA, is applied as an adjunct for a conjoint paradigm: The combination may not only disproportionately increase social support and reinforcement but may also stabilize progress outside the therapy sessions; the interpersonal perspective of PTSD is necessarily and naturally tackled in such an approach.

An integrative therapeutic manual aiming at incorporating MDMA-assisted sessions into the CBCT-procedure is currently under development (Candice Monson, personal communication, October 22, 2014).

*Acceptance and Commitment Therapy (ACT)*

ACT is another novel approach in behavioral therapies that does not rely on exposure but on systematically *refuting* negative thoughts and feelings. From the perspective of ACT, PTSD is a result of excessive and ineffective attempts to gain and maintain control over unwanted mental contents. The basic rationale of ACT seems well-suited for the treatment of PTSD:

> The methods used in ACT are specifically directed at decreasing the client's use of avoidance or escape strategies in coping with unwanted thoughts, emotions and memories and at increasing their acceptance of, or willingness to experience, these private events while engaging in previously avoided behavioral action.[75] (Orsillo & Batten, 2005, p.97)

ACT applies a holistic approach in that it doesn't only focus on symptom reduction but also encourages patients to increase experiential openness and "identify valued directions and goals in their lives and to commit to actions that are consistent with these values" (ib.) and is explicitly directed to increase quality of life.[76] However, up to now empirical support for the efficacy of ACT in the treatment of PTSD is lacking. Nevertheless, elements of ACT might prove useful for implementation into future MDMA assisted protocols – particularly in the non-MDMA (that is: non-exposure) sessions or later stages of the treatment process.

### *4.3.3 The state of PTSD treatment*

Generally speaking the state of PTSD treatment is inadequate.
Wittchen et al. (2009) remark: "Only a small fraction of all PTSD sufferers receive any treatment and still fewer receive even the most minimal threshold of adequate treatment. […] If treatment occurs at all, it occurs many years after PTSD onset."

[75] The 'acceptance' part of the treatment.
[76] The 'commitment' part of the treatment.

But not only is the coverage poor, also the efficacy of existing treatments is unsatisfactory. Only around 50% of those patients that undergo treatment achieve remission of symptoms after 2 years (Wittchen & Hoyer, 2011). While this means that PTSD regularly chronifies even when treated, it does not mean that existing treatments are essentially ineffective – it rather indicates that they are only effective in those patients that respond to them.
Regarding the shortcomings of current approaches, Mithoefer et al. (2011) conclude:

> Overall, the evidence for pharmacotherapy and psychotherapies […] indicates that existing therapies for PTSD are ineffective for between 25% and 50% of patients who enroll in clinical trials. An effective treatment that could reduce the substantial treatment failure rates associated with existing PTSD treatments is needed. (p.440)

# 5. On the application of MDMA as an adjunct in psychotherapy for PTSD

Successful psychotherapy for PTSD is required to tackle and reduce intrusions and flashbacks, dysfunctional cognitions, and avoidance behavior. Of course such a treatment will also have to resolve the comorbidities typical for PTSD patients.
Still higher aspirations on what can be regarded as a successful treatment will have to take salutogenetic ideas into account. Then ridding a patient of disabling symptoms is merely one part of the treatment; the other part is fostering posttraumatic growth towards a healthy, fully functional human being, capable of having loving relationships and pursuing a meaningful and self-determined way of life.

As outlined in chapter 4.3, the distinct set of symptoms seen in PTSD patients makes many patients inaccessible to even the most fundamental level of effective mental health support; those patients live in a subjectively perceived hopeless state where there seems to be no possibility of escape from the agonizing core symptoms of chronic PTSD.[77] It is the aim of this chapter to illustrate the potential of MDMA as a facilitator of successful, salutogenetic growth-oriented, and curative treatment even for resistant cases of PTSD.

To integrate MDMA into PTSD treatment a few questions need to be considered:
What effects of MDMA are potentially useful for PTSD therapy and psychotherapy in general? At which points are current treatment approaches inadequate, what are reasons for treatment failure? Which psychological and neurological parameters would have to be altered to improve efficacy of treatments? Which features should a drug to facilitate trauma focused psychotherapy have? And why could MDMA fit the bill?
This chapter will answer those questions.

[77] It is not uncommon for patients to refer to their condition as “hell” or “living dead”.

## 5.1 Effects of MDMA that are potentially useful for psychotherapy

In chapter 3 the effects of MDMA were discussed in detail. For the purpose of this chapter, a short recapitulation of assorted effects that may contribute to its efficacy as a psychotherapeutic adjunct is appropriate – note that some of these effects are not mentioned in chapter 3 as they stem from clinical experience rather than experimental inquiry:

*Psychological and behavioral effects*[78]

- profound well-being, euphoria
- unique anxiolysis
- feelings of empathy, sociability, interpersonal closeness, trust
- feelings of love and (self-)acceptance
- increased emotional sensitiveness and responsiveness
- positivity bias in the perception and processing of emotional and socio-emotional contents
- heightened openness
- psychophysical stimulation
- increased confidence
- mental clarity
- loosening of ego boundaries
- heightened state of awareness
- intensified perception, interoception, and introspection
- considerate social disinhibition, extraversion
- enhanced verbalization capabilities
- relaxation
- increased sensuality
- negligible impairment of cognitive and executive functions, mild side and after-effects, full recollection of events

[78] In rough order from a more emotional to a more cognitive to a more somatic nature of effects.

*Psychopharmacological and neuroendocrine effects*

- increased levels of serotonin, dopamine, and norepinephrine
- significant agonist action at 5-HT-receptors and the alpha2-adrenoreceptor
- increased levels of cortisol, prolactin, and oxytocin
- decreased activity in (limbic) brain regions associated with anxiety and fear response (medial temporal lobes, especially the amygdala), increased activity in regions associated with social reinforcement (ventral striatum), possible increase in activity in cortical regions that inhibit limbic activity (medial prefrontal cortex)

## 5.2 Psychotherapeutic rationale: explanations of MDMA's efficacy in PTSD therapy

Before presenting potential methods of improvement, I want to focus on obstacles and reasons for failure in PTSD therapy:

Confrontation, processing, and reconsolidation of the traumatic memory are in one way or another at the core of any successful therapy. The first common reason for ineffective treatment is that confrontation cannot be realized because the patient is – or assumes to be – unable to tolerate the overwhelmingly negative feelings that are associated with revisiting the trauma. Some patients may even reject the idea of (directive) exposure as part of their treatment plan.
The second problem is emotional engagement during confrontation: underengagement as well as overengagement prevent modification of the fear structure. In the former case detachment or emotional numbing prevent effective trauma activation and reprocessing; in the latter overactivation of the trauma causes overwhelming responses.

For both of those problems the level of perceived safety is crucial. This includes manifest variables in the treatment setting, the capacity of the therapeutic relationship, and the attitude of the patient. Typically a PTSD patient perceives the world as *completely dangerous*

and one's self as *completely incompetent*. However, only if the patient feels sufficiently safe, trusts the environment, and has the confidence to regain control and competence, the trauma can be overcome.
Rauch and Foa (2006) present a short illustrative vignette of a patient that was underengaged and detached because of intolerable fear:[79]

> The therapist then explained that it was really important to include the scary moments during the imaginal exposure, and focus on her personal thoughts and feelings. Ms. M then related her fear that if she talked about these scary parts of the memory she would "lose it." And the therapist reminded Ms. M of the rationale for imaginal exposure and reassured her that she was safe in the therapist's office. (p.63)

To encounter this underengagement, the therapeutic relationship needs to be strong enough for the therapist to convince the patient that she is in a safe place.
It's not surprising that in PTSD therapy there is an especially strong link between the strength of the therapeutic alliance and positive therapy outcomes (Charuvastra & Cloitre, 2008). At the same time PTSD patients often struggle with trusting and benefiting from interpersonal relationships.
From a more cognitive point of view the patient needs to be put in the present – *safe* – context and the trauma needs to be put in the context of the past. Potential negative cognitions towards social support ("No one can help me") need to be considered as well.

In sum: for successful therapy a patient must feel safe, confident, and have trust in the therapist(s). The patient needs to be both grounded and motivated to fully engage in the trauma without being overwhelmed. Unfortunately, for many patients these requirements cannot be met.

The question is: what can MDMA do to counter the pitfalls of PTSD therapy?
However, before bringing MDMA into this picture, it must be stressed that the field of MDMA-assisted psychotherapy research is very young and much that can be written on it is speculation based on clinical experience. Thus the following explanations should be seen as

[79] The method was prolonged exposure.

working hypotheses that warrant empirical backing and further theoretical groundwork.[80] For further illustration, a range of qualitative statements from participants in therapeutic trials is provided in the appendix (p.129ff.). The reader in encouraged to read those statements in conjunction with the following explanations.

MDMA assisted psychotherapy is conventional psychotherapy augmented by several (2-3) MDMA-assisted sessions. Exposure specifically takes place during the MDMA-assisted sessions.[81] The basic rationale of MDMA as an adjunct is that it widens the tolerable zone of engagement and thus enables the patient to fully embark in confronting the trauma without being overwhelmed. Under the influence of MDMA, the patient *is* detached, however not from the trauma memory but from the sense of imminent threat to the self that emanates from revisiting the trauma. The implication is that trauma activation, reprocessing, modification, and contextualization are often enabled in cases where confrontation seemed impossible. In addition emotional processing is sped up – sometimes dramatically.

In therapeutic settings, MDMA seems to create an *inherent* sense of safety:
It apparently has stabilizing effects on the therapeutic relationship[82] as it deepens the sense of trust and the willingness to open up and commit. This means that *less* emphasis has to be put on establishing the relationship because MDMA facilitates this process considerably; relationship building mainly happens during the first MDMA-session (Michael Mithoefer, personal communication, December 7, 2014).
Besides this external or interpersonal effect, it can also create the sensation of an *inner safe space*. The increased suggestibility that comes along with psychedelic drug effects (Carhart-Harris, Kaelen, et al., 2014) can be deliberately used to foster feelings of inner safety by attaching a semantic framework to them.[83]
The effects of MDMA on the psyche of the patient as well as on the therapeutic relationship, together with the carefully prepared setting create a radically novel learning context for the patient and resonate well with Ehlers and Clark (2000) notion of 'putting the trauma in the past'.

[80] It goes without saying that the ideas and implications in this chapter are *strictly* limited to controlled use in a highly structured clinical setting with therapeutic intentions. Generalization to other settings is inappropriate.
[81] N.B.: Exposure is spontaneous and *not* directive. See chapter 6.1.1
[82] See also chapter 3.5; MDMA reliably creates a positive bias to socio-emotional stimuli.
[83] E.g.: "You know you are in a safe place."

There are a few ‘secondary effects’, that at this point can only be backed by clinical experience but that are worth mentioning to get a better picture of the psychotherapeutic potentials:

Experiences occasioned by MDMA are often regarded as extraordinarily intense with a positive valence. Such experiences can be seen as an ‘inverse traumatization’, that is: an experience that is as intense, drastic, and far-reaching as a traumatic experience but with a positive valence. While this is certainly not the rule, such experiences are still regularly observed in therapeutic settings and usually result in a massive reduction of PTSD symptomatology. Generally, (profoundly) positive emotional states are possible but they are neither certain nor necessary for progress. The predominant – and most of the times inevitable – effect is a psychological ‘opening up’ and a nonspecific amplification of mental processes (cf. Grof, 1980). The direction of the ensuing experience is determined by the state of the psychotherapeutic process and careful guidance by the therapist(s).
The combination of anxiolysis, empathogenesis, and psychostimulant effects may even lead to the perception that *everything* is more accessible – commonly with a strong intrinsic motivation to deepen and intensify the inner process and also to verbalize and communicate.
Accordingly, the reduction of defensiveness towards repressed memory contents is not limited to traumatic memories. In many cases, the trance like state of MDMA provokes spontaneous recollection of memories that may stretch back until early childhood. This effect may aide in uncovering pretraumatic psychological vulnerabilities that resonate with the traumatic experience(s) and that are often the key to explaining the manifestation of PTSD. Comprehending these associations may help the integration of traumatic contents into a coherent and meaningful biographical narration.
Another important factor when it comes to a meaningful integration is forgiveness: PTSD sufferers often find themselves trapped between feelings of fear, rage, shame – and cognitions circling around inexpiable injustice, the desire for complete obliteration of the trauma, and a futile search for external atonement. MDMA’s capability to occasion an attitude of loving (self-)acceptance can enable patients to radically change perspective, reappraise, make peace, and find ways to forgive the people or circumstances responsible for their misery as well as themselves.

Table 7 summarizes common effects of MDMA in psychotherapy as observed by Oehen et al. (2013).

| Category | MDMA-induced state | Psychotherapeutic implication |
|---|---|---|
| Mood/Affect | Mild euphoria | Positive and fearless emotional state of well-being |
| | Anxiety and fear ↓ | Emotional avoidance↓ |
| | Enhanced perception of and intensified feelings | Tolerance and processing of difficult emotions ("window of tolerance")↑ |
| | Affect tolerance↑ | |
| Cognition/ Memory | More imaginative and associative | Recall of relevant traumatic memories↑ |
| | Contemplativeness↑ | Prolonged spontaneous exposure to traumatic memories |
| | Recall and tolerance of traumatic memories↑ | Cognitive restructuring |
| | | "simulation of alternative behavior" |
| Attachment/ Interpersonal Behavior | Social fears and defensiveness↓ | Improvement of therapeutic alliance |
| | Social approach behavior↑ with empathy, openness, trust, feelings of being connected to others↑ | Rebuilding of trusting relationships |
| | | Defensiveness and isolation↓ |
| | Cuddling and need for touch↑ | |
| Self | Self-esteem ↑ | Grounding/centering↑ |
| | Self-acceptance↑ | Consolidation of self↑ |
| Body | Release of muscular tension | Release of tension and reduction of somatic symptoms |
| | Analgesia | |
| | Sensuality↑ | Positive body image |

*Table 7. Psychological effects of MDMA in the context of psychotherapy (Oehen et al., 2013).*

## 5.3 The neuroscientific rationale

I want to start this chapter with a general remark: Although (psycho)pharmacological effects 'underlie' many psychological and behavioral effects, the explicatory power of the biological level of analysis may seem limited during a complex psychotherapeutic process. However, understanding this level is crucial and imperative not only for basic researchers but also for any potential practitioner.

Knowledge about the biopsychological principles of the MDMA induced state has some broader benefits:

- to help explain and cope with unusual or unexpected, wanted or unwanted psychological or somatic phenomena that may occur during a therapy session.

- to augment the pharmacological mechanism of action on the psychological level to utilize the MDMA induced state in an optimal way.[84]
- to contribute to basic knowledge about the safety and efficacy of MDMA assisted psychotherapy.

The following paragraphs will elucidate and substantiate some of the benefits of MDMA in a psychotherapeutic setting from the perspective of biopsychology/-psychiatry. Given the current state of research, much of the contents consist of informed speculation based on theoretical considerations.

The neurocircuitry model of PTSD was introduced in chapter 4.2. It states that hyperactivation of the amygdala, inadequate top-down control/inhibition by prefrontal structures (vmPFC) and resulting deficits in contextualization, an attentional bias towards threat, increased fear response, and impaired extinction result in PTSD symptoms.
There is some evidence that MDMA produces acute neurophysiological effects that could be described as an *inversion* of PTSD in healthy subjects. In several studies (see chapter 3.6) MDMA decreased activity in brain regions associated with anxiety and fear response; decrease in amygdala (re)activity seems to be a consistent effect. Increased activity in prefrontal inhibitory structures has also been found but those effects are less consistent.

This rationale may provide an opportunity to explain the anxiolytic effects of MDMA and the improved capabilities of PTSD patients to confront and process traumatic material under the influence of the substance. To clarify this topic, further investigation applying functional imaging on PTSD patients under the influence of MDMA is required.

The 'inversion model' is also reflected on a behavioral level: PTSD patients have increased reactivity as well as an attentional bias towards threat related stimuli; this bias is correlated with amygdala activity (El Khoury-Malhame et al., 2011). MDMA shows both inverse action on the amygdala as well as a bias towards *positive* stimuli. The influence of emotional states

[84] E.g., during a session a patient may still associate a neutral stimulus with the trauma (decontextualisation) but will not feel threatened by it due to MDMA's effect on the nervous system, namely the amygdala. Knowledge of phenomena like this gives room for unique therapeutic interventions. In this example, a possible continuation could be to challenge negative appraisal on base of the diminished fear response.

on the interpretation of ambiguous events is basic knowledge in CBT research; negative emotional states favor threatening interpretations (cf. Mathews, 2006). In this sense, a positive emotional bias can also have a more global effect on the modification of dysfunctional or biased cognitions – "seeing things in a different light".

Apart from the level of brain regions, acute effects on neuroendocrinology and neurotransmitters may also underpin some psychological and therapeutically useful effects: MDMA increases oxytocin levels, which is one factor for the unique empathogenic effects (Kirkpatrick, Lee, et al., 2014). Moreover, oxytocin in itself does also affect brain regions involved in the neurophysiological correlates of PTSD and is investigated as an adjunct for PTSD therapy (Koch et al., 2014).
Raised levels of serotonin at 5-$HT_{1a}$ and 5-$HT_{1b}$ receptors reduce feelings of depression and anxiety and increase self-confidence; agonist action at 5-$HT_{2a}$ receptors alters the perception of meanings, potentially leading to new ways of thinking about past experiences (Sessa, 2011). The release of dopamine, norepinephrine, and cortisol promotes arousal and alertness, what could influence motivation and engagement. Activity at alpha2-receptors prevents overstimulation and might be accountable for MDMA's seemingly paradoxical – and therapeutically useful – relaxing effects; prolactin secretion may also contribute to this effect (Passie et al., 2005). Furthermore, increased levels of norepinephrine could improve recollection of traumatic events[85] (Kemp, Lickel, & Deacon, 2014; Southwick et al., 1999) and raised cortisol improves fear extinction in psychotherapy (Dominique et al., 2011).

In sum the psychopharmacological profile, the psychological and prosocial effects as well as the duration of effects, the absence of serious adverse side or after effects, and resulting high tolerability make MDMA seem like an ideal agent to assist trauma therapy and encounter the main reasons for therapy failure.

[85] This effect may be attributed to the state-dependent memory phenomenon: memory retrieval is more efficient, when the context is similar to the context in which the learning experience took place. In this case, this common context is the increased level of NE both during the traumatic experience and the MDMA-induced state.

# 6. The status quo and future of MDMA assisted psychotherapy for PTSD

Chapter 5 described the continuity of conventional psychotherapy and MDMA as an adjunct; this chapter will describe some of the distinctive elements of MDMA-assisted psychotherapy for PTSD as well as existing results from completed therapy trials.

It is noteworthy that the non-profit research organization MAPS is responsible for practically all of the scientifically sound theoretical and practical work available today. MAPS has created and implemented a research protocol as well as a treatment manual and pursues the long term plan to turn MDMA assisted psychotherapy into an approved intervention until 2021 (Emerson et al., 2014). Although at the moment the engagement of MAPS is essential and presumably prolific, it is important that future research will also be carried out by institutions independent of MAPS and with different protocols. This chapter will focus on the approach developed by MAPS, as it seems to be the best practice for now.

## 6.1 The treatment manual developed by MAPS

### *6.1.1 Cornerstones of the manual*

On the psychotherapeutic level, the approach adopts established methods (TFCBT) and enriches them with:

a) humanistic concepts: in particular the patient is trusted to be the expert of his/her own healing process and the source of healing. Especially during substance assisted sessions the approach is non-directive: contents and processes that are crucial for healing are trusted to spontaneously come to surface with the right intensity at the right time. This fundamental conviction is actively fostered in patients. The therapists and the MDMA are seen as facilitators.

b) psychodynamic perspectives: the meaning and developmental history of the trauma as well as relationships, conflicts, and transference phenomena naturally come up during MDMA assisted sessions. Those contents are important for reprocessing, restructuring, and integration.

In the context of this thesis the details of the manual and research protocol cannot be discussed, instead some defining features and notable differences to other approaches will be pointed out. The following contents are taken from the paper by Mithoefer (2013b) as well as the *Manual for MDMA-Assisted Psychotherapy in the Treatment of Posttraumatic Stress Disorder* (Mithoefer, 2013a) [86] provided by MAPS.

*General features:*

- The approach consists of three stages: preparatory, substance, and integrative sessions.
- Three 90min preparatory sessions are followed by one MDMA-assisted session, followed by three integrative sessions, etc. With three substance assisted sessions, the treatment consists of 15 sessions in total.
- The treatment setting rather resembles a comfortable living room than a medical facility; however safety measures must be at hand.
- All sessions, including the MDMA sessions, are video-taped.
- Two therapists are present at all times.
- Possibility of 24/7 telephone contact with the patient between sessions and also during follow-up.
- If possible, the patients' social support network is included in the treatment.
- Primary care physicians and – in some cases – psychotherapists are informed.

[86] Retrievable at http://www.maps.org/mdma-research-timeline/4887-a-manual-for-mdma-assisted-psychotherapy-in-the-treatment-of-ptsd . Author's note: readers interested in the psychotherapeutic attitude and interventions throughout the different stages of the treatment are strongly encouraged to study the treatment manual.

*Introductory sessions:*

- The utmost emphasis lies on the creation of a safe setting – inner and outer.
- Similar to CBT, a relaxation technique is being taught to confront symptom exacerbations that may occur during, between, and after the treatment.
- Clarification of the option of physical touch during MDMA sessions, explicit affirmation of the nonsexual nature of possible physical interventions; agreement to a command to stop potentially unwanted interventions.
- There is no systematic trauma exploration before the first MDMA-session. The emphasis lies on resource activation and establishment of a therapeutic alliance. However, possible anxiety provoking triggers and defenses may be explored.
- Installation of a common therapeutic language/terminology. Suggestions are installed as a foundation of the inner space: 'Inner healing intelligence'; 'beginner's mind', introduction of 'the medicine'.
- Psychoeducation about the MDMA-induced state and the features of the 'medicine'. Particularly the patient is made familiar with the non-linear fashion of the healing process catalyzed by MDMA, taught to expect the unexpected, encouraged to 'surrender' to and accept whatever may arise as part of the healing process.

*Substance assisted sessions:*

- MDMA-assisted sessions last 6-8 hours and are two to six weeks apart; there are two or three sessions depending on protocol, the therapists' judgement, and the patients' decision on how to proceed. Three sessions seem to be superior for most patients (Michael Mithoefer, personal communication, December 6, 2014).
- Active doses range from 100mg to 187.5mg with supplemental dosing; 125mg is considered a full dose, however lower doses (100mg) are being investigated; doses are fixed and not based on body weight due to evidence of non-linear metabolism.
- During MDMA-sessions patients usually lay on a futon with one therapist on either side. But patients may move if they wish to.
- MDMA-sessions consist of alternating episodes of introspection and episodes of communication. The duration of the episodes depends on the individual process.

- MDMA assisted therapy for PTSD does also rely on (imaginal) exposure, but unlike established therapies, trauma exposition is *non-directive*: "The course of therapy is determined by the individual's own inner healing intelligence interacting with facilitation by the therapists in the context of the therapeutic relationship. […] Many of the therapeutic elements that are directly elicited by therapists in more established methods occur spontaneously with the less directive approach we use in MDMA-assisted therapy" (Mithoefer, 2013b, p.11). During MDMA- assisted sessions the trauma contents usually emerge spontaneously without therapeutic guidance.[87] However, patients are encouraged to return to the trauma, to 'get into', or even 'breathe into' the trauma to revisit and process those contents that distress them the most. In essence, the course of the substance assisted sessions is left to the patients' own healing intelligence.
- The patients are encouraged to work with physical sensations that may arise. If necessary and if the patient permitted it, somatic manifestations of the trauma and ongoing process are dealt with by either nurturing touch or focused bodywork.
- During introspective episodes, patients have the option to wear eyeshades and have the opportunity to listen to (a standardized set of) music, optionally through headphones.
- Music is used as a tool to support and guide emotional processing and lower cognitive barriers.
- The later parts of the session – that is after the peak effects subside – may be challenging for some patients. The therapists encourage patients to reflect, validate, and possibly verbalize the experience.
- After the MDMA session the patient stays overnight at the treatment facility.

*Integration sessions:*

- A follow-up integrative session occurs on the morning after the MDMA-assisted session.

[87] There is an agreement with the patient that the therapists can bring up the trauma if it doesn't come up spontaneously.

- Details of the preceding substance assisted session are discussed.
- Possible distress or cognitive dilemmas are addressed as part of the ongoing healing process.
- During integrative sessions, patients are prepared for and supported in the long-term period of integration, during which the benefits gained in the MDMA-assisted sessions are to be applied in daily life.
- If applicable, integration is followed by preparation for the next MDMA-assisted session.

### *6.1.2 Requirements for patients – inclusion and exclusion criteria*

The current target population in the MAPS studies consists of adult subjects who have been diagnosed with PTSD (CAPS score of 50 or higher) for more than 6 months and have failed to gain relief through approved PTSD treatments. For safety and evaluation patients have to undergo extensive medical diagnostics and psychodiagnostics.

The following paragraph shows the complete list of inclusion and exclusion criteria. This list is provided by MAPS and used in clinical trial protocols (cf. MAPS, 2012)[88].

*Inclusion Criteria:* Individuals eligible to be enrolled into this protocol are participants who:

1. Meet DSM-V criteria for current PTSD with a duration of 6 months or longer;
2. Have a CAPS score of *50* or higher, indicating moderate to severe PTSD symptoms;
3. Are at least 18 years old;
4. Have tried and failed to achieve relief from PTSD symptoms through X therapy [approved PTSD treatment].

[88] Retrieved at http://www.maps.org/research-archive/mdma/MP8_amend4_final_7Feb2012web.pdf

5. If in ongoing psychotherapy at the time subjects are recruited into the study, participants may continue to see their outside therapist during the course of the study. Participants must sign a release for the investigators to communicate directly with their therapist. Subjects may not change therapists, increase the frequency of therapy or commence any new type of therapy until after the evaluation session 3 months after the final experimental session. Subjects who do not live within reasonable driving distance of the study site (equal to or less than an estimated two hours' drive from the study site) must have a therapist in the area in which they live whom they can call on for support and evaluation if necessary;
6. Are willing to refrain from taking any psychiatric medications during the study period, with the exception of gabapentin when prescribed for pain control. If the subject is on stimulants for ADHD at baseline, they can continue to use them at the same dose and frequency as long as they discontinue 5 half-lives before each MDMA session and do not restart for 10 days after each MDMA administration. Any psychoactive drugs, including stimulants, will be tapered in an appropriate fashion to avoid withdrawal effects. Medications will only be discontinued after consultation with the prescribing physician;
7. Agree that, for one week preceding the MDMA session will refrain from:
    a) taking any herbal supplement (except with prior approval of the research team);
    b) taking any nonprescription medications (with the exception of non-steroidal anti-inflammatory drugs or acetaminophen unless with prior approval of the research team);
    c) taking any prescription medications (with the exception of birth control pills, thyroid hormones or other medications approved by the research team);
8. Agree to take nothing by mouth except alcohol-free liquids after 12:00 A.M. (midnight) the evening before the experimental session;
9. Refrain from the use of any psychoactive drug, with the exception of caffeine or nicotine, within 24 hours of each MDMA session;
10. Agree not to use caffeine or nicotine for 2 hours before and 6 hours after the dose of MDMA;
11. Are willing to remain overnight at the study site;
12. Agree not to drive until after noon the day following each experimental session;

13. Are willing to be contacted via telephone for all necessary telephone contacts;
14. Must have a negative pregnancy test if able to bear children, and agree to use an effective form of birth control during the treatment period, not including long-term follow-up;
15. Must provide a contact (relative, spouse, close friend or other caregiver) who is willing and able to be reached by the investigators in the event of a participant becoming suicidal;
16. Must agree to inform the investigators within 48 hours of any medical conditions and procedures;
17. Are proficient in speaking and reading *English* [or the respective native language];
18. Agree to have all clinic visit and integration sessions recorded to audio and video;
19. Agree to not participate in any other interventional clinical trials during the duration of this study.

*Exclusion Criteria:* Individuals not eligible to be enrolled into this protocol are those who:

1. Are pregnant or nursing, or are women of child bearing potential who are not practicing an effective means of birth control;
2. Have a history of, or a current primary psychotic disorder, bipolar affective disorder type 1 or, dissociative identity disorder;
3. Have evidence or history of coronary artery disease or cerebral or peripheral vascular disease, hepatic disease with abnormal liver enzymes, or any other medical disorder judged by the investigator to significantly increase the risk of MDMA administration;
4. Have hypertension using the standard criteria of the American Heart Association (values of 140/90 or higher assessed on three separate occasions);
5. Have liver disease with the exception of asymptomatic subjects with Hepatitis C who have previously undergone evaluation and successful treatment.
6. Have history of hyponatremia or hyperthermia;
7. Weigh less than 48 kg;
8. Would present a serious suicide risk, as determined through psychiatric interview, responses to C-SSRS and through the clinical judgment of the investigator, or who, in

the judgment of the investigator, are likely to require hospitalization during the course of the study;

9. Would present a serious risk to others as established through clinical interview and contact with treating psychiatrist;
10. Have used "Ecstasy" (material represented as containing MDMA) more than 10 times within the last 10 years or at least once within 6 months of the MDMA session;
11. Require ongoing concomitant therapy with a psychiatric drug;
12. Meet Diagnostic and Statistical Manual of Mental Disorders (DSM)-V criteria for active substance abuse or dependence for any substance save caffeine or nicotine in the past 60 days;
13. Are not able to give adequate informed consent;
14. Have any current problem or a history of substance abuse that, in the opinion of the investigator or medical monitor, might interfere with participation in the protocol.

### *6.1.3 Requirements for therapists – qualification and skills*

In the MAPS protocols, MDMA-assisted psychotherapy for PTSD is generally conducted by a team of two therapists. That is: one female, one male; one with a medical background, one with a psychological background.

As the approach is non-directional, therapists should have a client oriented basic attitude and a strong empathic presence (Mithoefer, 2013a). They have to be able to tolerate intense emotions, need to be familiar with altered states of mind and transpersonal/mystical experiences[89], they must not be afraid of extreme states and strong manifestations of the multiplicity of the psyche (i.e. transient personality split), furthermore they must not pathologize such states but need to have the skills to work with them (ib.). Last but not least, they need to have trust in the self-healing capabilities of the patient and must be able to

[89] Such experiences may be extremely valuable for healing but may also challenge the belief system of patients and therapists alike. Therapists do not need to understand or interpret such experiences but need to be able to help the patient integrate them in a manner that supports the healing process.

convey this conviction to the patient.

Experience in the treatment of PTSD is required, the background of therapists can be in Prolonged Exposure, Cognitive Processing, Eye Movement Desensitization and Reprocessing, and Psychodynamic Therapy; experience with other methods is valuable, e.g.: Holotropic Breathwork, Internal Family Systems, Voice Dialogue, Psychosynthesis, Hakomi, Sensorimotor Therapy, Holotropic Breathwork, Jungian psychology, Buddhist psychology, and Virtual Reality (Mithoefer, 2013a).

Since the early days of MDMA in psychotherapy, self-experience is considered an imperative part of therapists' training:

> He [Leo Zeff[90]] always insisted that any therapist who intended to make use of this magic drug had to try it in himself first. That has been the rule ever since, whenever healers wish to make use of either MDMA — which is not a psychedelic drug — or any of the true psychedelics in their therapy. The therapists *must* [sic] know the effects of any such drugs in themselves, before giving them to anyone else. (Stolaroff, 2004, p.18)

Today the legal framework for self-experience is lacking. Provisionally, MAPS has gained the allowance to administer a single dose of MDMA to 20 therapists as part of a phase-I placebo-controlled, double-blind, randomized cross-over study (Emerson et al., 2014).

## 6.2 Preliminary outcomes of the research sponsored by MAPS

Up to now, only three therapeutic trials have been completed but several more are currently in progress (NCT01958593, NCT01211405, NCT01793610, NCT01689740, NCT01404754[91]) or under development. The treatment manual is constantly improved and the relative efficacy of different approaches is investigated, especially regarding the optimal number of MDMA-

[90] See chapter 2.2.2

[91] Accessible under https://clinicaltrials.gov

assisted sessions and the dose(s) administered. All trials enroll patients who suffer from chronic treatment-resistant PTSD.

The exploratory trial by Bouso et al. (2008) was conducted to investigate the safety of different low doses (50 or 75mg) of MDMA; unfortunately the study had to be discontinued due to political pressure after six subjects had been treated. The treatment was psychologically and physiologically safe for all subjects.

The phase-II pilot study by Oehen et al. (2013) applied 125mg with a supplemental dose of 62.5mg and incorporated an 'active placebo' condition (25mg+12,5mg) to improve blinding. The sample size was small (12 patients) and there were no statistically significant reductions in CAPS scores for the MDMA versus active placebo group, but patients did report clinically significant self-reported improvements in PTSD symptom severity. Although the study was too underpowered for significant effects, effect sizes were *estimated* to be at 1.0 and 1.4 at long-term follow-up (Chabrol & Oehen, 2013). The treatment was considered safe, but the active placebo design didn't prove successful as it wasn't well tolerated psychologically and *increased* CAPS-scores.

Up to now, the phase-II trial by Mithoefer (2011)[92] was the largest and most rigorous. In stage 1 the trial enrolled 12 patients who received 125mg (+ optional supplement) of MDMA during two sessions and 8 in the placebo group; after the second experimental session 7/8 patients in the placebo group participated in open-label treatment with MDMA (stage 2). The last 8 subjects recruited also received a third MDMA-assisted session.
The patients enrolled in the trial had been suffering from PTSD for an average duration of 19.5 years. The clinical response (>30% reduction in CAPS scores) was at 83.3% in stage 1 and 100% in stage 2. The between group effects size was 1.24 and 2 months after the last MDMA-session 18/20 of the participants no longer met criteria for PTSD.

All 19 subjects who had received MDMA took part in the follow-up study (Mithoefer et al., 2013) 17-74 months after the initial trial. There were no statistical differences in CAPS scores obtained at study exit and at follow-up, however two subjects did relapse. These two

[92] Qualitative statements form this trial are provided in the appendix (p.129ff.).

patients took part in an unpublished 'relapse study' and experienced significant decreases in CAPS scores (Emerson et al., 2014).

Table 8 shows the CAPS scores of individual subjects over time.

| Study Group | Crossover | Pre-MDMA Treatment | After two MDMA sessions ("2-month" score) | After three MDMA sessions**** | LTFU | Number of months between the final MDMA treatment and LTFU CAPS |
|---|---|---|---|---|---|---|
| MDMA | | 43* | 16 | | 14 | 59.8 |
| MDMA | | 43** | 46 | 28 | 19 | 35.7 |
| MDMA | | 57 | 0 | | 3 | 65.7 |
| MDMA | | 65 | 29 | | 33 | 51.4 |
| MDMA | | 76 | 32 | | 18 | 74.3 |
| MDMA | | 78 | 2 | 0 | 0 | 18.1 |
| MDMA | | 89 | 79 | | | NA |
| MDMA | | 90 | 16 | 19 | 60 | 43.0 |
| MDMA | | 94 | 14 | | 20 | 55.2 |
| MDMA | | 102 | 60 | | 7 | 46.3 |
| MDMA | | 103 | 6 | | 91 | 66.0 |
| MDMA | | 113 | 4 | 2 | 18 | 17.3 |
| Placebo | Yes | 64*** | 15 | | 10 | 40.7 |
| Placebo | Yes | 65*** | 27 | 34 | | NA |
| Placebo | Yes | 70*** | 41 | 29 | 31 | 19.8 |
| Placebo | Yes | 78*** | 42 | 19 | 24 | 27.7 |
| Placebo | Yes | 84*** | 42 | 21 | | NA |
| Placebo | Yes | 85*** | 21 | | 17 | 57.6 |
| Placebo | Yes | 86*** | 49 | | 14 | 50.4 |
| | | ***Post-Psychotherapy only, Pre-MDMA | | **** 3rd session occurred following "2-month" outcome scores | | |

"NA": not applicable, as the CAPS were not completed at LTFU by these three subjects.
*CAPS at enrollment was 56, prior to medication washout. In order to provide support during the washout period, subjects received non-drug preparatory psychotherapy, which may have led to transient decreases in PTSD symptom severity. To be conservative, the authors chose to report the post-washout CAPS scores in the initial paper and the same convention was used in this paper. **CAPS at enrollment was 62, prior to the medication washout. CAPS: clinician-assisted PTSD scale; LTFU: long-term followup; MDMA: 3,4-methylenedioxymethamphetamine; PTSD: post-traumatic stress disorder.

*Table 8. Global CAPS scores of individual PTSD study subjects (Mithoefer et al., 2013)*

Table 9 summarizes the features and outcomes of completed clinical trials.

| Reference (Year), Trial Type | Patient Number | Treatment Groups | Treatment Regimen | Primary Measure | Results (MDMA vs Placebo) |
|---|---|---|---|---|---|
| Bouso et al (2008),[24] R, DB, RC | 6 | MDMA 50-75 mg (n = 4); placebo (n = 2) | MDMA or Placebo given during one 6-hour experimental psychotherapy session | SSSPTSD | • MDMA vs placebo SSSPTSD baseline: 40.0 ± 7.0 vs 44.5 ± 7.1<br>• SSSPTSD post therapy: 29.3 ± 8.7 vs 40.0 ± 1.4<br>• SSSPTSD R E baseline: 12.8 ± 3.2 vs 12.5 ± 7.1<br>• SSSPTSD RE post: 11.0 ± 4.5 vs 12.0 ± 1.4<br>• SSSPTSD A baseline: 16.8 ± 2.6 vs 15.0 ± 2.8<br>• SSSPTSD A post: 11.0 ± 4.1 vs 16.0 ± 0.0<br>• SSSPTSD AI baseline: 10.5 ± 3.1 vs 14.0 ± 1.4<br>• SSSPTSD AI post: 7.3 ± 1.7 vs 12.0 ± 0.0<br>• SSSPTSD SS baseline: 24.3 ± 9.3 vs 25.0 ± 4.2<br>• SSSPTSD SS post: 17.3 ± 8.7 vs 18.5 ± 13.4<br>*P* values not calculated because of small patient numbers, different MDMA doses administered, and unequal distribution between groups |
| Mithoefer et al[27] (2011), R, DB, PC | 23 (Three MDMA patients did not complete therapy) | MDMA 125 mg (n = 12); placebo (n = 8) | MDMA or placebo given during two 8-hour experimental psychotherapy sessions | CAPS | • MDMA vs placebo CAPS baseline: 79.2 ± 6.6 vs 79.6 ± 8.1<br>• CAPS session 1: 37.8 ± 8.4 vs 74.1 ± 10.3<br>• CAPS session 2: 29.3 ± 6.5 vs 66.8 ± 8.0<br>• CAPS 2 months post: 25.5 ± 7.7 vs 59.1 ± 9.4<br>Group vs time interaction showed greater improvements for MDMA than placebo ($P = 0.015$) |
| Mithoefer et al[27] (2011) single arm, OL (OL study of Mithoefer et al[27] above) | 7 | MDMA 125 mg (n = 7) | MDMA given during two 8-hour experimental psychotherapy sessions to those previously given placebo | CAPS | • Baseline vs MDMA CAPS baseline: 65.6 ± 24.4<br>• CAPS 2 months post MDMA: 33.9 ± 12.8<br>CAPS scores significantly reduced with MDMA use versus baseline in patients previously receiving placebo; $P < 0.05$ |
| Mithoefer et al[28] (2013), single arm, OL (OL extension study of Mithoefer et al[27] above) | 19 (3 Participants did not complete the long-term follow-up questionnaire) | MDMA 125 mg (n = 16) | Comparison of long-term follow-up results of patients given MDMA versus 2 months post-MDMA therapy | CAPS | 2 Months post-MDMA vs 17-71 months Post-MDMA<br>• CAPS 2 months Post-MDMA: 23.7 ± 22.8<br>• CAPS long-term post-MDMA: 24.6 ± 18.6<br>CAPS scores post-MDMA similar in the short and long term; $P = 0.91$ |
| Oehen et al[29] (2013), R, DB, AC | 14 (2 Participants dropped out of the trial, 1 per arm) | MDMA 25 mg + 12.5 mg 2.5 hours later (n = 4); MDMA 125 mg + 62.6 mg 2.5 hours later (n = 8) | MDMA or placebo given during three 8-hour experimental psychotherapy sessions | CAPS | High dose vs low dose<br>• CAPS baseline: 66.4 ± 13.6 vs 63.4 ± 7.9<br>• CAPS session 2: 63.0 ± 17.8 vs 60.0 ± 6.8<br>• CAPS session 3: 50.8 ± 19.7 vs 66.5 ± 7.6<br>Trend toward greater effects from higher-dose MDMA; 2-way ANOVA $P = 0.066$ |

*Table 9. Clinical Trials of MDMA in PTSD (White, 2014)*

## 6.3 How to bring MDMA assisted psychotherapy to the patients – licensing MDMA as an approved drug

The aim of MAPS as a non-profit pharmaceutical company is to develop MDMA as a prescription drug[93] until 2021 through the standard procedure of drug development (Emerson et al., 2014). This means that MDMA has to undergo phase-II and phase-III clinical studies approved by the U.S. Food and Drug Administration (FDA). If those studies are successful, MDMA could be approved by the FDA and subsequently by the European Medicines Agency (EMEA) as a prescription medicine.

Currently two phase-II trials have been completed and several phase-II trials are in progress. If those studies further prove the safety and efficacy of the treatment, multi-centric phase-III trials will be implemented. Phase-III trials would be conducted with approximately 200 subjects; two trials are typically required (ib.).

Phase-III has to demonstrate whether the protocol is consistently safe and effective in different (cultural) contexts with different therapists. It also has to clarify which doses of MDMA and which therapeutic interventions are the most effective. As future investigators and therapists need to gain experience with the procedures, several proof of concept studies will have to precede large scale phase-III trials.

[93] However, MDMA cannot be a medication that any physician can prescribe. Its application must be limited to specifically trained and licensed experts (see chapter 7.1.3).

# 7. Discussion

## 7.1 Issues of an MDMA-assisted treatment of PTSD

While MDMA may seem like a well-suited facilitator of trauma therapy, the approach faces a number of specific methodical, theoretical, and practical issues. Some of the currently most prominent topics will be discussed in this chapter.

### *7.1.1 Methodical issues*

Today the randomized controlled trial (RCT) is considered the gold standard in the investigation of medical or therapeutic interventions. Generally, a RCT reduces a complex problem field into a set of small quantifiable indices and investigates relationships between those variables. Random assignment to either a (placebo) control or an experimental group is the core of a RCT and any medication has to pass a set of RCTs to be approved by regulatory authorities. The methodology of those trials is relatively rigid and research on MDMA-assisted psychotherapy faces a few specific challenges in face of those regulatory procedures. This chapter will discuss a few of those challenges.

a) General problems

There are a few problems specific for PTSD therapy research that are potentially aggravated by the addition of MDMA:

- Naturalistic samples of PTSD patients are notoriously ‘dirty’: Patients experienced simple or complex traumatization, they suffer from various comorbidities, some have dissociative tendencies, others don’t – the efficacy of MDMA assisted psychotherapy is potentially altered by those factors, which may lead to unchecked distortions in outcome data, especially if sample sizes are small.
- Those patients with the most severe pathology could also profit the most from MDMA-assisted psychotherapy, but they may also be potentially unfit for informed consent.
- Potential samples are further narrowed by specific contra-indications: all psychiatric medications need to be tapered off; active substance abuse or dependence is prevalent in chronic PTSD patients and leads to exclusion ; all patients with CNS, CVS, hepatic or renal issues need to be screened out; (*potential*) pregnancy is a strict contraindication; all patients with comorbidities in the psychotic spectrum a have to be excluded at the current stage of knowledge; the same goes for patients with comorbid borderline personality disorder, bipolar I disorder as well as dissociative identity disorder. However, dropout rates can expected to be relatively low due to increased commitment to a novel and promising treatment approach.

These objections can be encountered or compensated. However, there are two methodological concerns that stem from the conflict of applying the standard procedure of pharmaceutical trials and the peculiarity of psychotherapy with psychoactive substances:

b) Inherent research bias and the blinding problem

Clinical investigation and licensing of MDMA as a medication has to undergo the same procedure as any other pharmacologically active substance. However, psychotherapy with psychoactive substances is neither a pharmacological nor a psychotherapeutic paradigm. It is a combination of both and as such cannot be reduced to the pharmaceutical action of the adjunct. What is being tested, is the efficacy of an elaborated therapeutic paradigm and not the efficacy of a substance. As a direct result, simple dose-response trials are obviously of limited value. The clinical response is not necessarily correlated with the total dose

administered.

The two main concerns stem from this inherent entanglement of psychotherapy and psychopharmacology:

1. Experimenters – that is: therapists conducting the trial – are *necessarily* biased towards the conviction that the paradigm works. Their therapeutic actions are inseparable from the pharmaceutical action of the substance. If they didn't *believe*[94] in the healing potential of the pharmaceutical aide, they could not conduct the trial in a way that is ethically and medically sound. While this objection may sound trivial, it would classify as a severe limitation in a standard pharmaceutical trial. This is a fundamental bias and could only be avoided with a radically different methodology that isn't guided by standard licensing procedures.
2. The second serious methodological concern is closely related: The action of strong psychoactive substances is extremely hard to blind for both researchers and patients. Clinically relevant doses of psychoactive substances such as MDMA have effects on consciousness (usually obvious for subjects), behavior, and physiology (usually obvious for investigators) that are prominent enough to compromise blinding and effective placebo control. Successful blinding under all conditions would imply that patients show an extremely strong placebo response (or an extremely weak pharmaceutical response respectively) and/or therapists show a worrying lack in empathy and situational awareness. Accordingly, blinding in trials applying inactive placebo versus a full dose of MDMA fails consistently (cf. Carhart-Harris, Kevin, et al., 2014; Hysek et al., 2014; Mithoefer et al., 2011).

   In therapeutic trials however, there are arguments against placebo effects being responsible for outcome differences: there is an independent rater who remains blinded, group differences are maintained at follow-up, and efficacy is reported in patients who were treatment-resistant before the trial (Mithoefer et al., 2011).

   Still the problem is fundamental in nature: simple placebo vs. experimental group designs necessarily fail in these trials.

   Two potential solutions for this problem have been proposed:

[94] In this context it is also noteworthy that self-experience is generally regarded as *imperative* among therapists, who work with psychoactive substances.

The first one is the application of an *active* placebo (25mg of MDMA), which unfortunately has resulted in undesirable therapeutic effects in patients[95] (Oehen et al., 2013) and could unsystematically confound effect sizes – *primum non nocere* applies here and active placebo conditions, including other pharmacologically active substances 'mimicking' MDMA, should be avoided in therapeutic settings.
The second possibility is the application of dose-response schemes with 2 or 3 conditions; e.g. 75mg vs. 100mg. vs 125. Such an approach would leave out a control group but would potentially result in successful blinding; additionally it would provide important data for the relationship of dose and therapeutic efficacy. Studies relying on this approach have already been approved and are currently being conducted (cf. Emerson et al., 2014).

At this point a short excursion seems adequate:
The effects of any pharmacologically active substance – psychoactive or not – can be divided into a *pharmacological response* and a *meaning response* (Moerman & Jonas, 2002). The pharmacological response is determined by the interaction of the biochemical properties of the substance and the (neuro)physiology of the subject, the meaning response however is much more complex to grasp.

Placebos do not 'cause' a placebo effect as they are inert and don't cause anything by definition but they still have an effect. Moerman and Jonas (2002) ascribe the placebo effect to the *meaning* that is 'attached' to the placebo. E.g.: If an inert 'anti-headache' tablet with a widely advertised brand name on it does in fact reduce headaches, the effect does not emanate from the inactive tablet but rather from the brand name. The subjects show a meaning response. Obviously meaning is not only attached to medications by themselves but to all kinds of information that surrounds us: "[…] man is an animal suspended in webs of significance he himself has spun" (Geertz, 1973, p.5). In a medical context this includes anything from the appearance and behavior of the medical professionals, to the characteristics of the treatment room, to the physical properties of the medication (shape,

[95] Patients may experience sympathomimetic effects without the therapeutically useful anxiolysis, which puts them in risk of uncontrolled trauma activation and retraumatization.

size etc.), and also the (momentary) internal representations in the patient, including expectations, presuppositions, memories, emotions, cognitions etc.
A distinguishing feature of substances with psychedelic properties, such as MDMA, is that they intensify the perception of meaning. Grof (1980) dubbed them "amplifier[s] of mental processes […] something like the microscope or telescope of psychiatry" (p.297). Accordingly, their effects are commonly much more determined by variables of set and setting than by their pharmacological properties. The pharmacological effects rather constitute a projection screen for a meaning response. The effects they display are rather "sociopharmacological"[96] (Jungaberle & Röske, 2004, p.33) than pharmacological and therefore volatile.[97]

In practice, these properties are not a hindrance but a crucial factor for their potential as psychotherapeutic tools. They are even the base of therapeutic work with the assistance of those substances: The substances amplify the 'webs of significance' that are spun by psychotherapeutic methods and rituals. The therapeutic response can in fact be seen as a special case of the placebo response – it is an intensified, controlled, and targeted meaning response.
If this chain of thought is applied to the methodology of drug trials, the methodical issues appear in a different light: Psychotherapeutic methods and rituals, the interactions and processes that take place in this framework are presumably much more important to understand the effect-factors and outcomes of therapy with psychoactive substances than any (quasi-)pharmacological cause-and-effect reasoning (cf. Moerman, 2011). The psychopharmacology is indeed necessary to explain the effects on the psychological level, but it rather enables a process than determines an effect.
It is obvious that what can superficially be seen as a 'bias of the therapist' does in fact constitute his/her efficacy. The call for blinding does even seem absurd with this reasoning in mind. Inert placebos do cause a meaning response, but this response is vanishingly slight compared to the meaning response caused by substances with psychedelic properties.

[96] In this regard, those substances resemble media that are subject to a dynamic and diverse cultural reception (cf. Slunecko, 2008).
[97] However, the effects of MDMA are relatively more consistent than those of classic psychedelic substances. See chapter 3.2.1

Going back on a rather practical level, a consequence of those sociopharmacological properties is that the skill, personality, experience of therapists, and adherence to treatment manuals is a major factor for the outcomes of therapy trials with psychoactive substances. The external validity is bound to be lowered in principle, trials are inherently harder to compare. It thus seems highly questionable if therapy with psychoactive substances can be treated with the same protocols as 'classic' interventions.

Clearly some of the methodical problems cannot be completely solved under the given circumstances and this fact makes this research vulnerable for criticism that seems justified from established perspectives. The fact that randomized controlled trials are the basis of drug development, licensing, and comparisons of relative efficacy, should not lead to the false conclusion that a complex psychotherapeutic method can be treated exactly like a pharmacological intervention.[98] By all means, perceived methodical limitations should not be an impediment for research – especially in view of the evidence that the treatment yields promising results in former treatment-resistant patients.

Finally, at the present time (qualitative) research on therapeutic processes in psychotherapy with psychoactive substances has barely been conducted. Such research is necessary as it will help elucidate therapeutic mechanisms and encounter limitations in other methodical areas.

[98] This objection holds true for all psychotherapy research that relies on RCTs (cf. Bergin & Garfield, 1994), however it is aggravated in the case of psychotherapy with psychoactive substances, where an actual pharmacological intervention is part of the treatment *as well*.

### *7.1.2 Theoretical issues*

a) Lack of theoretical understanding of the healing mechanisms

There is growing evidence that psychotherapy with MDMA is effective for the treatment of PTSD but it is not yet clear enough *how*. As shown in chapter 5, the psychological and (neuro)physiological effects of MDMA can be – at least partially – aligned with the neurophysiology, pathology, treatment, and healing process of PTSD. The acute MDMA-induced state can in some ways be described as inverse PTSD – the major concern is how it is possible that those beneficial effects last even after the medicine has left the organism. One could even argue that therapeutic progress under the influence of MDMA is a case of state dependent learning and should be accordingly *inefficient*. To the contrary, patients undergoing MDMA assisted therapy often make – relative to the duration and persistence of their disorder – extremely rapid, drastic, *and* lasting progress. Progress that should not only be reflected on the psychological and behavioral level but also on the neurophysiological level: MDMA could be an agent that radically catalyzes (emotional) learning processes and that promotes neuroplasticity. However, at this point one cannot even speculate about the mechanisms underlying these processes.

b) Controversy about risks and dangers

Lack of knowledge about the mechanism of the therapeutic effects of MDMA can be encountered with more research efforts; however, a minority of researchers still regards MDMA-assisted psychotherapy as highly controversial in principle. MDMA's *potential* to produce acute and long-term toxic effects has led some researchers to conclude that "there are no safe clinical applications for MDMA" (Capela et al., 2009, p.212); others fight personal wars against the therapeutic use of MDMA (Parrott, 2007; Parrott, 2013, 2014). In the latter case the absence of even the most basic understanding of the paradigm or intentional misrepresentation due to a preference of moral over scientific arguments, respectively, is apparent (cf. Doblin et al., 2014). Today the majority of researchers who write about MDMA,

but are not primarily interested in its therapeutic potential, stress the need for additional research (cf. Degenhardt & Hall, 2010; White, 2014).

Opponents of MDMA in psychotherapy usually criticize that application of the substance is not "safe" and therapy research is, therefore, objectionable. The statement that MDMA is not "safe" is unquestioningly correct but the conclusion is not: The use of MDMA has acute and chronic risks and unwanted effects, as is the case with *any* pharmacologically active substance.[99] A primary aim of any therapeutic paradigm is to assure safety, to find valid answers to valid concerns, to register and minimize risks, to weigh carefully whether the potential benefits justify those risks that cannot be excluded and finally, to identify ways to minimize potential harm that emanates from unchecked risk factors.
In the case of MDMA and PTSD, there is ample evidence that the application of therapeutic doses in controlled settings is *sufficiently* safe[100] and at least some evidence that the benefits are sufficiently strong[101] to justify the paradigm. After all, the risks of MDMA-assisted psychotherapy must be weighed against the risks of chronic PTSD.

Practically, the potential acute risks of MDMA can be minimized by screening out patients carrying risk factors (e.g., cardiovascular diseases) and by excluding environmental risk factors (e.g., high ambient temperature). Additionally, regular patient monitoring and continuous availability of medical care are further elements of risk-minimization.
Regarding long-term damage there is no direct evidence at this point that suggests that therapeutic dosing regimens are detrimental in any kind. But again: the potential risks, as low or high as they might be, must be weighed against the detrimental effects of living with treatment-resistant PTSD.

In conclusion, MDMA assisted psychotherapy has *acceptable risks* but is not "safe".
A treatment utilizing MDMA in psychotherapy assumes that – as well as in any other

[99] Pharmaceuticals with severe physical and mental risks are routinely prescribed and researched on a daily basis; e.g., opiates used in pain management have a low therapeutic index and inevitably cause dependency, millions of doses of psychostimulant drugs (e.g., ritalin or adderall) with similar physical effects as MDMA are taken daily, countless pharmaceuticals with known potentially dangerous and/or unpleasant effects are researched in volunteers without any intent for therapeutic application and last but not least millions of patients *depend on* psychopharmaceutical maintenance medication with often minimal efficacy but documented side effects and health risks.
[100] See chapter 3.4
[101] See chapter 6.2

approved medical treatment – the benefit justifies the risk. Specifically, chronic maladaptive behavior and high levels of psychological and physiological stress have more severe consequences than possible acute or long-term toxicity present in a treatment that could potentially eradicate all risk associated with prolonged mental suffering.

c) Possible informal use of MDMA by former patients

Another – unrelated – objection that is sometimes brought up against MDMA in psychotherapy is the reinforcing nature of the substance. Patients might seek it out to alleviate their symptoms and consequently become 'addicted'[102] to MDMA (or other illicit substances). This objection most likely stems from the invalid generalization of 'ecstasy-phenomena' to the therapeutic setting, the association with traditional concepts of psychopharmacological maintenance medications and fundamental misconceptions about the reality of the therapeutic process under the influence of MDMA. Clinical experience and evidence show that patients are usually rather deterred by the idea of confronting themselves with the MDMA-induced state without proper guidance and preparation:

> Only one participant, who had received two[103] MDMA-assisted psychotherapy sessions, reported the subsequent use of "ecstasy" in a quasi-therapeutic setting, on a single occasion before the LTFU [long-term follow-up]. Attempting a therapeutic setting similar to the study by asking a friend to be present during the session, the subject found the arrangement unsatisfactory and so reported no interest in repeating it outside a legal therapeutic context. (Mithoefer et al., 2013, p.32)

and

> The data we obtained about illicit drug use from the LTFU Questionnaire supports the hypothesis that MDMA can be administered in a clinical setting with minimal risk that the subjects will subsequently seek out and self-administer "street ecstasy", or become

[102] N.B.: In general there is limited evidence for the existence of an MDMA dependence syndrome (Degenhardt & Hall, 2010).
[103] Three sessions seem to be optimal.

> dependent on the drug. This is consistent with the comments from many study subjects, who expressed the strong opinion that the therapeutic setting and close follow-up were essential elements of the treatment, and they did not think MDMA should be used without this level of clinical monitoring and therapeutic support. (p.34)

In fact, successful treatment naturally reduces the urge to numb and self-medicate with intoxicants that is prevalent in PTSD patients. Yet, possible informal use of MDMA after treatment completion should be specifically investigated if MDMA-assisted therapy is taken towards phase-III studies.

### *7.1.3 Practical issues*

a) Responsibility for matters of public health

The last objection in the previous chapter (informal use) points towards one of the main practical issues: It is quite striking that the core of the theoretical controversy surrounding MDMA in psychotherapy does not actually deal with 'MDMA in psychotherapy' but with 'Ecstasy and public health'. In the present paper, a clear separation of "ecstasy" and MDMA as well as recreational and therapeutic use has been attempted – as is scientifically sound. If the necessity for this separation is intentionally or unintentionally disregarded, the discourse becomes heavily confounded with debris from the war on drugs. (Attempted) Therapeutic use is automatically associated with sensation seeking, high risk taking, health decline, loss of control, and deviant or delinquent behavior etc. Moral arguments corrupt scientific arguments, political and ideological propaganda corrupt scientific investigation. However, there *is* a responsibility to deal with some of the epiphenomena of the war on drugs when researching the psychotherapeutic potential of psychoactive substances. While it is my personal conviction that such a researcher should not be specifically

concerned about the 'drug discourse'[104], there lies an inevitable responsibility in the actions, publications, and attitudes of such a researcher: research does influence the public and research that is popular and controversial does so even more.
Unfortunately, therapeutic research with psychoactive substances might convey misconceptions that could put people at risk. Public health must be a concern of any medical or therapeutic practitioner. Thus it is a responsibility of researchers to minimize potential social risks and, at best, convert them into chances.

The statement that MDMA-assisted psychotherapy has acceptable risks means not that this risk profile is generalizable to any context, any dose, in any subject, with any intention. Equally, the statement that MDMA has shown to be effective for the treatment of PTSD does not mean that MDMA is a 'fire-and-forget silver bullet' for any mental health disorder. To professionals this may sound trivial – but unfortunately it is not. To illustrate this issue I would like to present a short vignette, taken from the comments section of a popular science website. The corresponding article announced that a new MDMA trial is approved.

> "*What the actual fuck*!!!!! I tried it for the first time after reading something similar and I spent the next *two months in bed*! Doctors couldn't find anything wrong other than the fact that it triggered my pre-existing anxiety to a severely high level where I was constantly over stimulated! Topping it off I developed panic disorder, it's coming up to 5 months since it happened and I'm practically half the person I used to be, scared to go places & do certain things, scared to live a normal life. And it's all thanks to MDMA!" (retrieved from: http://www.iflscience.com/health-and-medicine/trial-will-investigate-use-mdma-treatment-anxiety-seriously-ill-patients [emphasis in original])

Regardless, whether or not the self-medicator in this example did in fact consume MDMA[105] – he/she apparently had a severe adverse reaction and required medical care after reading about the benefits of MDMA in therapeutic settings and therefore deciding to "try it". This is a very vivid example of how research in this field inevitably influences public perspectives on psychoactive substances and may promote risky and potentially harmful behavior. How can

[104] That is: recreational use, abuse, and impact of psychoactive substances in general as well as the legal, political, and socio-economic framework surrounding the phenomenon.
[105] The reaction does not sound atypical. A combination of inadequate preparation, wrong expectations, absent guidance, an unfavorable setting, a high dose, missing or poor integration may very well produce the described symptomatology.

this be prevented?

The concept of MDMA assisted psychotherapy is surely much too complex for the general public, but it can be made clear that set and setting are actually more important for beneficial outcomes than the psychoactive substance and that self-medication attempts must therefore be strongly advised against. Maybe MDMA should not be depicted as a medicine but as a *psychotherapeutic tool* that can only be reasonably handled by experts.

Notwithstanding, people *will* keep consuming MDMA both for recreational and therapeutic reasons. And if research raises awareness for potentially therapeutic effects, more people – presumably the most desperate ones – will seek out these effects. And as authorized possibilities are still to be established, they will do so in illicit and informal settings and bring themselves at risk, which consequently evokes a moral dilemma for research. In this specific case one can only provide adequate information and refer to personal responsibility.

In general, research can certainly not legitimate uncontrolled use but psychotherapy with psychoactive substances is the ideal positive model for integrative and adaptive use of psychoactive substances – substances that can be harmful if used irresponsibly. In this light, research could help reduce risks and harms associated with uncontrolled use by promoting the most basic needs for awareness, preparation, responsibility, and integration when dealing with strong psychoactive substances.

For the time being, some moral dilemmas are unavoidable but it should have become clear that therapy research with psychoactive substances is one side and objective and neutral education about the risks and benefits of psychoactive substances is the other side of the same coin.

b) The challenge to find and train enough capable therapists

One strength of the treatment with MDMA is that it creates a strong ritual context and puts the patients in a state of increased suggestibility. Subtle priming in preparatory sessions and targeted suggestions during substance assisted sessions *can* be used to guide the patients towards an optimal therapeutic process – on the other hand this means that patients are

significantly more manipulable and therapists are significantly more powerful than in classic psychotherapy. It is obvious that this feature demands for utmost integrity and professionalism on the side of the therapists.
The cult leader, guru or charlatan who drugs his/her subordinates to make them pliable and dependent is almost a cliché. A contemporary and striking example is the Swiss psychiatrist Samuel Widmer who underwent a transition from respectable physician and researcher with an interest in therapy with psychoactive substances to quasi-cult leader, with a loyal following (cf. Jungaberle et al., 2008, p.90ff.). This cult, with the combination of people in mental distress in search for salvation, psychedelic substances, an extreme interpretation of sexual liberty, and a charismatic leading figure, can quite rightly be seen as a worst case scenario regarding professionalism. Circumstances like those are essentially abusive and provide a prototypical example of what professional psychotherapy with psychoactive substances is *not*.

Generally, strong psychoactive substances themselves have an inherent charisma that may seduce some to develop dogmatic constructs around the experiences those substances occasion and subsequently develop hierarchical social structures that resemble formal religions. It goes without saying that such tendencies must be compensated by careful selection and thorough training of potential therapists.

Even without worst case scenarios in mind, there a few specific challenges:
Most notably therapists need expert knowledge about both psychotherapy and psychopharmacology and therapists need the skills to endure, deal with, and integrate extreme states in patients.[106] After all, a core feature of substances like MDMA is *intensification*, which may also lead to a massive but transient aggravation of pathological features. Specifically in the treatment of PTSD severe dissociation right up to personality split is not ruled out – a therapist needs to know methods to work with those states. Similarly, transference phenomena are intensified as well.

In addition to exceptionally strict character requirements, therapists obviously need extraordinarily *broad* knowledge as well as extraordinarily *specialized* knowledge, high

[106] N.B.: Being mere *witness* to such extreme states does also have to be integrated on the side of the therapists.

flexibility, outstanding intuition, and situational awareness. Accordingly, a future problem will be to find and train enough capable therapists. Another consequence is that substance assisted psychotherapy cannot and must never be a standard intervention, that any therapist can apply. The approach must be limited to specifically trained and licensed experts (and evidence based manuals).

To alleviate some of the mentioned challenges, existing protocols always employ therapist teams (male/female, medicine/psychology-background). Given the increased intensity and complexity of (some) sessions, video recording is standard, intervision and supervision are exceptionally useful.

All those factors favor specialized treatment centers over private practices. The issue of training therapists can be tackled with a 'co-pilot-approach', similar to the training of commercial airline pilots, with a veteran therapist and an apprentice working together.

c) Costs and funding

In light of the preceding paragraphs, it should be clear that this treatment approach is relatively expensive: Training is sophisticated, substance assisted sessions are long, the substance itself is an additional cost factor, two therapists are present, the overnight stay at the therapy site further rises the costs, manuals are complex – however, in the long run effective but expensive treatment is more efficient than lingering illness accompanied by ineffective treatment.

For now the more pressing problem is not the cost of therapy, but the costs of *research* on MDMA-assisted therapy:

Conducting studies is disproportionately expensive, especially because authorization and production of *Good Manufacturing Practice* (GMP)-MDMA is costly.[107]

However, one crucial problem is, that MDMA is not patentable and consequently no profit-oriented pharmaceutical company is interested to sponsor its research (cf. Greer & Tolbert, 1986). As a result, investigators have to rely on donations and/or crowd funding –

[107] The manufacturing costs of 1kg of GMP-MDMA are in the range of 800.000$. N.B.: With a maximum of three full dose+supplement treatment sessions this means that the costs of the MDMA are at 450$ per patient.

approaches that are extensively being employed by MAPS, which is currently the only organization funding clinical trials. MAPS does also conduct clinical research and MAPS-members act as investigators, which leads to inevitable conflicts of interest. At the moment this methodical concern cannot be avoided for practical reasons.

## 7.2 Opportunities

### *7.2.1 General therapeutic working mechanisms in MDMA-assisted psychotherapy*

MDMA-assisted psychotherapy displays some features and seems to have some potentials that are radically new in the field of mental health. However, even effect-factors that distinguish this novel approach are not impalpable and can to some extend be sufficiently explained with general therapeutic working mechanisms.

Grawe, Donati, and Bernauer (1994) describe five basic mechanisms for change in psychotherapy (cf. Grawe, 1997, 2004b):

1. *The therapeutic bond*: The quality of the relationship between therapist and patient is a crucial factor for therapeutic progress.

2. *Problem actuation*: A problem can most effectively be changed when it is experienced, that is when the patient comes into direct contact with painful emotions or conflicts.

3. *Resource activation*: Patients must be ready and capable for change, therefore their positive potentials, their healthy and competent parts as well as their strengths, skills, and social support networks etc. must be activated

4. *Mastery*: Generally a patient in distress is seen as *not-being-able*-to-do-otherwise. In therapy the patient must learn to cope with difficult or painful situations, thus the therapist must help the patient to develop self-efficacy. The very *experience* of mastery is a key factor for change.

5. *Motivational clarification*: The patient must gain insight into the meaning of his/her state; that is: what are the origins and maintaining factors of the problematic state he/she is in.

According to Grawe (1997) "[t]he effectiveness of a given form of therapy is a function of the extent to which these mechanisms of change are activated by concrete therapeutic procedures […]" (p.4). While all effective therapies apply those mechanisms to a certain extent, MDMA specifically augments every single one of them.

The therapeutic bond is directly increased due to empathogenic effects; problem actuation – which is especially challenging for PTSD patients – and resource activation are also inherent to the MDMA-induced state and can be further augmented by therapeutic techniques.[108]

The experience of mastery and motivational clarity is often strong *during* substance-assisted sessions. In general, the mechanism of mastery is typically more pronounced in training based methods (CBT) and less pronounced in psychodynamic methods that have an emphasis on clarification. During MDMA-assisted sessions, those two factors might actually merge: the often profound broadening and shift of perspectives may lead to such a radical modification of motivations and intentions that mastery over the trauma may seem trivial. In this reference system the trauma is simply transcended.

However, there is an obvious discrepancy between the strongly ritualized substance-assisted sessions and the everyday life of patients. As a consequence, mastery and clarification are mechanisms that must be addressed during integrative non-substance sessions. The experience of mastery during substance assisted sessions must specifically be trained to be applied to everyday life.[109] Clarification during substance assisted sessions is often non-

[108] See chapter 6

[109] The statement of a patient exemplifies this issue: "I'm not sure I can reach it again without MDMA but I'm not without hope that it's possible. Maybe it's like having an aerial map so now I know there's a trail."

verbal, experiential, and implicit; integrative therapy sessions (may) have to explicate those contents towards a lasting modification.
In light of these thoughts, it seems that MDMA-assisted therapy may inherently bridge the 'schism' between cognitive-behavioral and psychodynamic methods.

The gap that MDMA-assisted psychotherapy evidently bridges, is the one between psychotherapy and psychopharmacology. Research on the use of psychopharmacological agents such as MDMA to specifically augment psychotherapeutic working mechanisms and catalyze psychological and neurobiological processes is only just beginning. Still most of the questions that are currently being posed to this novel approach from the field of mental health can be answered – however, many of the really interesting questions have not even been asked yet. Not only are the lines between psychotherapy and pharmacology blurred, the lines between psychotherapy and spirituality are also heavily challenged. At present time and in this context, the spiritual, the mystical, the transpersonal perspective, which is more typically than exceptionally the frame of reference for people under the influence of substances like MDMA (cf. Griffiths et al., 2006), can be disregarded – for practical reasons. Currently those experiences are simply not present in the terminology and not part of the conceptualization of mental health sciences. However, future research into these novel methods will have to face and explore the clinically evident fact that some form of 'spiritual experience' is a therapeutic working mechanism. A mechanism that is as elusive as it is fundamental.

For now, from the perspective of present-day psychotherapy, the focused and intensified neurobiological and psychological transformation that can be observed during an MDMA-assisted therapeutic process is profoundly non-trivial. In fact, MDMA-assisted psychotherapy – and psychotherapy with psychoactive substances in general – might prove to be a radical game changer in psychiatry and psychotherapy.

(Mithoefer, 2013b, p.13) Staying with the metaphor, the following therapeutic process would be about 'learning how to hike'.

### *7.2.2 Further indications of MDMA assisted psychotherapy*

MDMA-assisted therapy is potentially useful for indications where anxiety and subsequent avoidance hinder the processing of emotional contents. The empathogenic effects also make it seem well suited for indications with a strong interpersonal component. Accordingly, MDMA is currently being investigated for the treatment of anxiety associated with life-threatening illness[110] and in the treatment of social anxiety in adults on the autistic spectrum (Danforth, Struble, Yazar-Klosinski, & Grob, 2015).

MDMA could also prove useful in indications that have an 'emotional numbing' component, such as substance abuse (cf. Jerome, Schuster, & Yazar-Klosinski, 2013) or borderline personality disorder. In borderline patients MDMA-assisted therapy sessions could potentially be effective during the later stages of Dialectic Behavioral Therapy (Linehan, 2014). It can further be speculated that the sense of loving self-acceptance typical for the MDMA phenomenology could be useful in the treatment of body dysmorphic disorder and eating disorders.

### *7.2.3 Challenges to the biopsychiatric paradigm and MDMA assisted psychotherapy*

The preceding chapters should have rebutted the assumption that MDMA-assisted psychotherapy is inherently dangerous and incompatible with evidence based psychotherapy. In fact, psychotherapy with MDMA as an adjunct is in many – but not all – ways neither a radically new nor a radically different approach but rather an enhancement of approved interventions. But for the greater part, psychotherapy with psychoactive substances in general is still met with disapproval.

While there is a number of practical specifics that distinguish the approach from classical interventions, it is the *uncanny* entanglement of psychopharmacology and psychotherapy

[110] Retrieved from http://www.maps.org/index.php?option=com_content&view=category&id=381

that challenges a few traditional values and convictions of psychiatry on a fundamental level and provokes opposition.

The trivial view on the condemnation of substances like MDMA in psychiatry is that those substances are almost consistently seen in a pathological and abuse oriented light. The notion of those 'drugs of abuse' as psychotherapeutic tools and medicines seems simply out of place.
But why is that the case? Especially as there are numerous 'dual-use substances'[111] that are at the same time condemned as recreational drugs and cherished as valuable medications. Why are drugs like MDMA not part of the psychiatric toolbox?

Current psychiatric medications dampen symptoms by their pharmacological action. They are meant to be taken chronically[112] – if the pharmacological action subsides, the symptoms often reoccur. Following this, the predominant psychiatric paradigms rely on a bottom-up view of the psyche, where human experience emerges from and is largely determined by 'underlying' (cf. Reardon, 2014) biological processes.[113] Accordingly, mental disorders are ascribed to 'mechanic' malfunctions of biological systems – and thus they should be treated by fixing or compensating those malfunctions on the same biological level.
On the other hand, psychotherapy with psychoactive substances relies on the biopsychosocial approach and postulates that human experience and behavior, including pathologies, stems from the complex interaction of biological factors and environmental factors with a sentient, competent, and self-empowered mind. From this perspective, bottom-up and top-down processes are equally important to both explain and treat pathologies. Thus, pathologies can be seen as a sort of communication disorder or a disintegration between biological functions, environment, and psyche.
They *do* have biological correlates but they also have behavioral correlates that alter environmental factors and vice versa; e.g., in the case of PTSD avoidance behavior massively decreases environmental variance and the potential for novel learning experiences. PTSD does also have mental and emotional correlates, such as hopelessness, perceived

[111] Opiates such as morphine, psychostimulants such as ritalin, dissociative anesthetics such as ketamine etc.
[112] Which is also expensive, increases the possibility for side effects, requires strong commitment by patients and in many ways – including withdrawal symptoms – resembles drug dependence.
[113] The indispensable reliance on animal models that are treated like biomechanical systems encourages this view in biopsychiatry.

incompetence, disconnectedness, fear, anger, shame, sadness, and terror. However, the psyche cannot only witness but also orchestrate this potpourri of stimuli and reactions.
A rationale of psychotherapy with psychoactive substances is to combine bottom-up and top-down processes and empower the psyche to heal itself *with the help of* purposeful and focused biological manipulation, not *by* quasi-technical manipulation of a hypothetical underlying biological correlate.
It seems that the pharmacology of substances like MDMA *somehow* provides an opportunity for extraordinarily fast learning processes. Psychologically, they temporarily alter seemingly rigid basic functions and open an unforeseen 'inner space'.[114]
In last consequence this space allows the mind to alter its own 'underlying' biology by meaningful reprocessing. Extremely rapid and *lasting* healing processes are *only* possible when the right mental actions are initiated. And after all, the consequence of those healing processes must also have biological correlates – correlates that cannot be explained by *transient* pharmacological action.
In essence, therapy with evocative psychoactive substances denounces mechanistic bottom-up views in favor of a conception of the human being as a capable entity that is able to accept the responsibility for his/her actions and fate.

It is quite evident that those concepts reach far beyond the damping of individual symptoms and towards the idea of a holistic healing process, a reintegration of neuronal and psychological processes in direct reference to the idea of *consistency* by Grawe (2004a).

While maintenance medications may *dampen* singular symptoms, substances like MDMA could be curative in a way that promotes self-healing capabilities. This implies that they are not an external intervention that can be passively consumed. Strictly speaking they do not cause an effect but they initiate a process, they do not erode self-efficacy (cf. Kemp et al., 2014) but they fundamentally rely on self-efficacy. In a therapeutic process, MDMA and related substances are meant to evoke challenging cognitive and emotional material; fostering and guiding self-efficacy towards a transformational process when facing this material may be a core task of professional therapists.

[114] This metaphorical 'inner space' is constituted of a – potentially radical – expansion and alteration of imagery, emotionality, sensuality, and cognition.

It seems like some of the paradigms of contemporary psychiatry are incompatible with the paradigms of psychotherapy with psychoactive substances, which may help explain the controversy surrounding this approach.[115]

However, the problem is not only an intrascientific conflict of paradigms, particularly in the case of PTSD it also has a cultural perspective. In this context I can only point to this problem: The massive and widespread psychopharmacological 'stabilization' of trauma patients is also an expression of the dialectic of the traumatizing society in the sense of Herman (1997) who puts this eloquently enough to quote her at large:

> The ordinary response to atrocities is to banish them from consciousness. Certain violations of the social compact are too terrible to utter aloud: this is the meaning of the word unspeakable.
>
> Atrocities, however, refuse to be buried. Equally as powerful as the desire to deny atrocities is the conviction that denial does not work. Folk wisdom is filled with ghosts who refuse to rest in their graves until their stories are told. Murder will out. Remembering and telling the truth about terrible events are prerequisites both for the restoration of the social order and for the healing of individual victims.
>
> The conflict between the will to deny horrible events and the will to proclaim them aloud is the central dialectic of psychological trauma. People who have survived atrocities often tell their stories in a highly emotional, contradictory, and fragmented manner that undermines their credibility and thereby serves the twin imperatives of truth-telling and secrecy. When the truth is finally recognized, survivors can begin their recovery. But far too often secrecy prevails, and the story of the traumatic event surfaces not as a verbal narrative but as a symptom. (p.1)

A society that literally stabilizes trauma on a large scale instead of processing and integrating it may remain functional, many do even profit, but it is not healthy.

[115] On a deeper level the controversy implicitly revolves around the fundamental question if natural science is adequate to understand the mind; that is the relationship of mind and matter.

## 7.3 Limitations

A general limitation of this thesis is that a number of conclusions are vague, some theories are presented with a caveat of missing evidence. However, this is inevitable in a paper that – in essence – explores a young and emerging field of research. The prevailing conclusion is that more research is needed.

More 'technical' topics, namely the combination of psycho- and pharmacotherapy, its novelty value, and its pitfalls, have been extensively discussed in this paper – the narrations, the meaning, the literal *context* surrounding trauma and traumatization has been left out or has only been lightly touched.

The context of the traumatic memory was merely mentioned in light of the abstract concepts of cognitive psychotherapy. On closer examination, adaptive recontextualisation in the sense of cognitive psychology means that the trauma is woven in a coherent and meaningful narration of a patient's biography. The trauma has to make sense in the area of conflict between the individual and the society that *allowed* the traumatization. What could not be elaborated in the present paper, are the actual contents of those narrations and their interconnectedness with social and political frameworks.

However, what must not be forgotten is that trauma is culture-bound: trauma needs victims, trauma needs perpetrators[116], and trauma needs social conditions where it can flourish (cf. Herman, 1997). Where trauma is seen apart from those social conditions, where trauma is at worst reduced to a biological malfunction or individual weakness, than the concept of PTSD becomes a vicious metaphor that serves to hide the fact that people are hurting people. People do not "suffer from PTSD", they suffer from violence and harm to their integrity as human beings.

A PTSD therapist must serve the individual but must also always reflect the social relativity of traumatic suffering and the societal and political implications of his/her actions.[117]

A topic that also fell victim to the pragmatic approach in this thesis is the level of (individual) psychotherapeutic processes. The reader interested in this topic has to rely on the limited

[116] That is: non-accidental trauma.

[117] The latter is especially relevant in the treatment of war veterans, where funding comes from the military.

and implicit insight that can be derived from the subjective accounts given in the appendix (p.129ff.). As there are no published case studies or qualitative analyses at this time, the topic warrants an own extensive research paper.

A closely related issue is the question to which extent established methodology – namely standardized quantitative methodology (e.g., CAPS scores) – is suited to investigate psychotherapy with psychoactive substances. It is quite obvious that psychotherapeutic processes and effect-factors are generally hard to grasp with quantitative methodology. But particularly in patients under the influence of MDMA, the inner process is commonly extremely focused and manifested – a data source which is compelling for qualitative research. Such research might actually transcend therapy research and may provide basic insights about consciousness and psychopathology.

But quantitative analysis may also be insufficient to assess the *outcomes* of MDMA-assisted psychotherapy. Presumably MDMA-assisted psychotherapy brings about clinically and especially personally significant effects that are not effectively grasped with standardized clinical tools. Future research will have to consider the more 'exotic' effects that exceed the scope of the DSM and focus on the salutogenetic perspective of psychotherapy with psychoactive substances.

These topics hint towards the philosophical and cultural perspective on altered states of mind in general and the healing power of those states in specific – issues which could not be tackled in this thesis.

Another necessary limitation of this thesis is the focus on the psychoactive substance MDMA and the indication PTSD. It is important to note that therapeutic research with other psychoactive substances and other indications is conducted too; for example classic psychedelic substances such as LSD and psilocybin are being investigated as an adjunct in the treatment of anxiety in patients with life-threatening illnesses (Gasser et al., 2014; Grob et al., 2011), addiction (Bogenschutz et al., 2015; Johnson, Garcia-Romeu, Cosimano, & Griffiths, 2014; Sessa & Johnson, 2015), obsessive compulsive disorder (Wilcox, 2014), and depression (Baumeister, Barnes, Giaroli, & Tracy, 2014; Carhart-Harris et al., 2012).

The choice of the models used to describe the pathology and treatment of PTSD was also the product of pragmatic reasoning. The emotional and cognitive processing theories and derived interventions were used as *one* possible and convenient approach towards the main

goal of the thesis, which was to explore links of psychotherapy with psychoactive substances and 'mainstream' psychology/psychiatry. The scope of this thesis was not to provide an *exhaustive* but a *convincing* picture. Potentially promising subjects, such as EMDR or psychodynamic approaches, were therefore disregarded.

The 'big picture' of psychoactive substances, especially the political and legal framework, the ethical and social implications, especially in light of the particular ambivalence of 'dual-use substances', have not been discussed to the extent that the topic calls for. I trust other researchers to elaborate those issues.

# 8. Conclusion

The main goal of this thesis was to explore the potential of psychotherapy with psychoactive substances for contemporary mental health services. MDMA was presented as an exceptionally well-suited substance for this endeavor. However, the turbulent history of the ambivalent substance that is MDMA obfuscates an unprejudiced and rational view on its potential as a medicinal substance. In fact, MDMA is an illegalized drug. The cultural product "ecstasy" is consumed by millions of people for a variety of purposes. It has the potential to occasion toxic effects and some people who use it suffer detrimental consequences from its uncontrolled consumption. People who are in contact with MDMA face criminal law and social stigma. This thesis demonstrated that researchers who wish to explore its medical potential cannot and must not avoid dealing with this cultural baggage.

On the other hand, MDMA is a 'dual-use substance' like many others that are commonly used in medicine. It can be used for non-medical purposes as well as medical purposes.
As shown, MDMA has a range of effects that are potentially useful for psychotherapeutic purposes: its trademark empathogenic effects, its unusual anxiolytic properties, its – at the same time – stimulating and relaxing nature, its tendency to foster self-acceptance and openness, its ability to amplify mental processes.

PTSD was described as a complex and agonizing, but relatively well-understood disorder. The treatment of PTSD is difficult and unsuccessful in many patients, which leads to a significant population of chronic sufferers that currently have to rely on 'palliative psychiatric care'. The major pitfall of psychotherapeutic treatment of PTSD is that effective therapy relies on trauma exposition and many patients are unable to confront their traumatic memories. Avoidance in face of the trauma is the core symptom *and* major maintaining factor of PTSD and it is also the main lever for MDMA-assisted psychotherapy. Under therapeutic guidance, MDMA reduces the overwhelming negative emotions associated with revisiting the trauma and potentially enables patients to engage in reprocessing and reintegrating their traumatic memories. At the same time, MDMA has beneficial effects on the therapeutic alliance.
This thesis also described the underlying neurobiology of both PTSD and MDMA. This line of thought underpins the psychological phenomena observed in therapeutic trials through the

notion of the psychopharmacological effects of MDMA as ‘inverse PTSD’. Most notably, MDMA reduces the excessive amygdala response.

While at this time there is no evidence for any long-term neurotoxic effects of MDMA in therapeutic regimens, MDMA has acute physical effects that may produce harm. Many of the known risk factors can be easily excluded from therapeutic settings, however vulnerable patients – the main concern is cardiovascular problems – need to be screened out from MDMA-assisted treatment and medical help has to be within reach at all times.
It can be concluded that the risks of MDMA in clinical settings and in therapeutic doses are justified by the potential efficacy of the treatment.

Besides these safety concerns, a major concern of the practical implementation of MDMA-assisted psychotherapy is the relative complexity of the treatment and the high standards that need to be demanded of future therapists. It became clear that MDMA-assisted psychotherapy requires highly trained experts and presumably specialized treatment centers.

This thesis has dedicated considerable space to the fact that MDMA-assisted therapy is not a pharmaceutical intervention but a combination of psychotherapy and psychopharmacology. This entanglement leads to a multitude of methodical and theoretical issues that will have to be discussed in the future. Equally important are the unique and exceptional effects of MDMA and other substances with psychedelic effects: the so-called transcendent, the mystical, the spiritual experiences that these substances seem to occasion with an astonishing reliability (cf. Griffiths et al., 2006). It is safe to assume that those states will have to be investigated as an undeniable effect-factor for the healing potential of psychotherapy with psychoactive substances (cf. Majic, Schmidt, & Gallinat, 2015).

The promising results of completed therapeutic trials and the theoretical considerations presented in this paper justify the conclusion that MDMA cannot be disregarded by the medical community. The example of MDMA and PTSD has demonstrated that therapy with psychoactive substances can be effectively applied with an acceptable risk-benefit ratio in the course of a manualized treatment, that it is probably a viable option for a range of other psychiatric indications, and that it can be sufficiently backed by evidence – evidence that is increasing day by day.

The actual potentials of psychotherapy with psychoactive substances still have to be grasped but it can be assumed that in the long run the approach is capable of revolutionizing the field of mental health with widespread consequences on society as a whole.

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# List of figures



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# List of abbreviations

| | |
|---|---|
| 5-HT | serotonin |
| ACT | Acceptance and Commitment Therapy |
| ACTH | adrenocorticotropic hormone |
| ADHD | Attention Deficit Hyperactivity Disorder |
| AVP | arginine vasopressin |

| | |
|---|---|
| BAC | blood alcohol concentration |
| CAPS-5 | Clinician-Administered PTSD Scale for DSM-5 |
| CBCT | Cognitive-Behavioral Conjoint Therapy |
| CBF | cerebral blood flow |
| CBT | Cognitive-behavioral psychotherapy |
| CNS | central nervous system |
| COMT | catechol-O-methyltransferase |
| CVS | cardiovascular system |
| CYP2D6 | debrisoquine 4-hydroxylase |
| DA | dopamine |
| dAAC | dorsal anterior cingulate cortex |
| DEA | Drug Enforcement Administration |
| DHEA | dehydroepiandrosterone |
| DSM | Diagnostic and Statistical Manual of Mental Disorders |
| EMCDDA | European Monitoring Centre for Drugs and Drug Addiction |
| EMDR | Eye Movement Desensitisation and Reprocessing |
| EMEA | European Medicines Agency |
| FDA | U.S. Food and Drug Administration |
| fMRI | functional magnetic resonance imaging |
| GMP | Good Manufacturing Practice |
| HPA | hypothalamic-pituitary-adrenal |
| IES-R | Impact of Events Scale-Revised |
| LSD | lysergic acid diethylamide |
| LTFU | long-term follow-up |
| MAO | monoamine oxidase |
| MAPS | Multidisciplinary Association for Psychedelic Studies |
| MDA | 3,4-Methylenedioxyamphetamine |
| MDMA | 3,4-methylenedioxy-N-methylamphetamine |

| | |
|---|---|
| mPFC | medial prefrontal cortex |
| NE | norepinephrine |
| OCD | Obsessive Compulsive Disorder |
| OTC | over the counter |
| OXT | oxytocin |
| PE | Prolonged Exposure |
| PET | positron emission tomography |
| PO | per os; oral administration |
| PTSD | Posttraumatic Stress Disorder |
| RCT | randomized controlled trial |
| RSFC | Resting-state Functional Connectivity |
| SÄPT | Schweizerische Ärztegesellschaft für Psycholytische Therapie |
| SCID | Structured Clinical Interview for Axis I Diagnosis |
| SCL-90-R | Symptom Checklist 90-Revised |
| SERT | serotonin transporter |
| SNRI | serotonin–norepinephrine reuptake inhibitor |
| SSRI | selective serotonin reuptake inhibitor |
| TFCBT | Trauma-Focused Cognitive-Behavioral Psychotherapy |
| UNODOC | United Nations Office on Drugs and Crime |
| vmPFC | ventromedial prefrontal cortex |
| WHO | World Health Organization |

# Appendix

## Abstract

Psychotherapy with psychoactive substances is a topic with a long and controversial history. Due to cultural and legal reasons, as well as theoretical and practical concerns, the possible therapeutic potential of some psychoactive substances has been disregarded by the medical community for the last decades. Today academic interest in the topic is on the rise: advances in psychopharmacology and increasing evidence of the safety and efficacy of some substances with psychedelic properties open up new perspectives for the stagnant treatment of mental disorders. This thesis explores the topic by the example of MDMA in the treatment of PTSD. A thorough examination of the history, effects and risk profile of MDMA is conducted. Based on existing evidence, the apparent potential of the substance is merged with contemporary models of PTSD and its treatment. The cornerstones of an existing treatment manual and outcomes from completed therapy trials are presented as well. Psychotherapy with the assistance of psychoactive substances faces some specific methodical, theoretical and practical issues which are critically discussed. The thesis concludes that MDMA-assisted therapy for PTSD is a viable option that deserves further investigation.

## Abstract [in German]

Das Thema Psychotherapie mit psychoaktiven Substanzen kann auf eine lange und kontroverse Geschichte zurückblicken. Auf Grund kultureller und rechtlicher Rahmenbedingungen sowie theoretischer und praktischer Vorbehalte wurde das mutmaßliche therapeutische Potential mancher psychoaktiver Substanzen während der letzten Jahrzehnte von der medizinischen Fachwelt missachtet. Derzeit erfährt das akademische Interesse an diesem Thema einen Aufschwung: Fortschritte im Bereich der Psychopharmakologie und zunehmende Evidenz bezüglich der Sicherheit und Wirksamkeit mancher Substanzen mit psychedelischen Eigenschaften eröffnen neue Perspektiven im stagnierenden Behandlungsangebot psychischer Störungen. Die vorliegende Diplomarbeit nähert sich dem Thema anhand des Beispiels MDMA-gestützter Psychotherapie bei PTBS. Die Geschichte, die Wirkung und das Risikoprofil von MDMA werden umfassend untersucht. In der Folge wird das mutmaßliche

therapeutische Potential der Substanz auf Basis vorliegender Evidenz mit zeitgenössischen Modellen der PTBS und deren Behandlung zusammengefügt. Die Eckpunkte eines existierenden Behandlungsmanuals und Ergebnisse bisher abgeschlossener therapeutischer Studien werden ebenso dargestellt. Die für Psychotherapie mit psychoaktiven Substanzen spezifischen methodischen, theoretischen und praktischen Probleme und Herausforderungen werden kritisch diskutiert. Die Arbeit kommt zu dem Schluss, dass MDMA-gestützte Psychotherapie eine realistisch umsetzbare Option bei der Behandlung der PTBS darstellt und weitergehende Erforschung angezeigt ist.

## Qualitative statements from the MAPS-trials

All the following accounts are taken from sessions during the trial by Mithoefer et al. (2011). Qualitative statements from this trial are provided in the treatment manual (Mithoefer, 2013a), the supplemental material to the follow-up study (Mithoefer et al., 2013), and in the paper by Mithoefer (2013b). Although there are many more accounts from (formal and informal) therapy sessions, limiting the material to this source has the advantage that all participants underwent the same protocol – that is the same treatment manual, setting and initial dose of 125mg.[118] The statements will be briefly labelled but are meant to stand for themselves. Readers are invited to read the statements as a complement to chapter 5 and 6.

*Perception of MDMA's mode of action by PTSD patients:*

> "I keep getting the message from the medicine, 'trust me.' When I try to think, it doesn't work out, but when I just let the waves of fear and anxiety come up it feels like the medicine is going in and getting them, bringing them up, and then they dissipate." (Mithoefer, 2013b, p.12)

> "The medicine just brought me a folder. I'm sitting at this big desk in a comfortable chair and the medicine goes and then rematerializes in physical form bringing me the next thing—this is a folder with my service record. It says I need to review it and talk to you about it from the beginning so it can be properly filed." (Mithoefer, 2013b, p.13)

*About trauma confrontation:*

> "I felt deeply connected to painful feelings of the traumas as I saw them go by in spheres, but it didn't cause anxiety. I felt deep sadness in my heart, [crying] but also deep happiness that I was healing it and letting it go." (Mithoefer, 2013a, p.41)

[118] However, some received a supplemental dose, while others didn't. Supplemental doses usually don't intensify but prolong the MDMA induced state.

> "I see huge white doors with beautiful white glass, so huge and heavy, but a master has engineered them so you can open them with one hand. It's only without the fear that the doors are so light. How interesting! If I go up to them with all the fears it makes me weak. I'm taking those fears out of different parts of my body, looking at them and saying 'it's OK but I'm leaving you here.' The fear served me well at one time, but not now for going through these doors." (Mithoefer, 2013a, p.41)

> "It's like, every time I go inside I see flowers and I pick one, and that's the thing to work on next. And there are things that are hard to take, but each time I move through them it feels so much better." (Mithoefer, 2013b, p.13)

*About overcoming dysfunctional cognitions:*

> "I don't think I would have survived another year. It's like night and day for me compared to other methods of therapy. Without MDMA I didn't even know where I needed to go. Maybe one of the things the drug does is let your mind relax and get out of the way because the mind is so protective about the injury." (Mithoefer, 2013a, p.57)

*Spontaneous cognitive restructuring, recontextualization, and validation:*

> "I feel like I'm walking in a place I've needed to go for so long and just didn't know how to get there. I feel like I know myself better than I ever have before. Now I know I'm a normal person. I've been through some bad stuff, but…those are things that happened to me, not who I am…This is me, the medicine helps, but this is in me." (Mithoefer, 2013b, p.13)

*About 'breathing into' the process and keeping rationalization/avoidance at bay:*

> Participant: "I feel really restless."
> Therapist: "Just try to go with the flow with that energy for a little while."
> Therapist: "I think it might be good to lie down, sink into the mattress, and let your body get comfortable with that movement if you need to. Try and let your breath take you into the confusion and let the medicine work as you breathe and take you through it."
> Participant: "If you don't mind, could you remind me to breathe into it? Just give me a little sign to breathe."
> Therapist: "How about if I just touch your shoulder to remind you? Remember the words, 'Don't get ahead of the medicine.' Let the medicine take you where you need to go." (Mithoefer, 2013a, p.37)

*Decreased defensiveness/increased accessibility:*

> "It feels almost like the inner healer or the MDMA is like a maid doing spring cleaning. It's as if you thought you were cleaning before but when you got to things you didn't really want to deal with you'd just stick them in the attic. If you're going to clean the house you can't skip the stuff in the attic." (Mithoefer, 2013b, p.14)

*Vignette about accessing childhood memories and recognizing the trauma as a part of an overarching narration:*

> Therapist: "You were beginning to sense the fear."
> Participant: "It changed from fear to 'I'm really mad at myself for allowing it to happen.'"
> Therapist: "Is that easier to feel than the fear?'
> Participant: "I guess so."

Therapist: “Because you were experiencing that and the fear began to come up and I invited you to go inside and feel the fear. How long before it switched to the anger?”
Participant: “Not long at all.”
Therapist: “Do you think your mind does that to distract you from the feeling of fear.”
Participant: “That’s possible. After the initial, ‘What the hell is going on,’ my mind clicked into ‘This is not happening. This is just too absurd to be happening’ … all the way back to when I was little … I never felt protected, really. There’s never been any support. I wasn’t free to be me … just what the situation called for. I had to do it then too, be what the situation called for.”
(Long silence)
“I feel like a lot of this baggage I’ve been carrying around I put onto myself – either disappointment in myself or self-blame. Don’t get me wrong, I don’t think I deserved it or asked for it or did something to bring that on. I don’t feel that way at all. It’s like your baseline and you’ve got your self-doubt, desperation on top of that, and before you know it, you’ve got a seven-layer burrito. I can feel every one of them. I don’t know how to express it or articulate it but I can feel every one of them. It’s not the ‘Yuck’ that I used to describe. They’re stacked one on top of the other. I guess I have just done it for so long that when the rape happened, it was the straw that broke the camel’s back. I just left. My mind said that’s enough, no more.” (Mithoefer, 2013a, p.34)

*A vignette about how a profoundly positive experience can lead to a shift in perspectives and insight:*

In her first MDMA-assisted session, this particular participant started with a Subjective Units of Distress (SUD) rating at 7/7.[119] She reported being very anxious about the unknown, including fear that flashbacks would be triggered. Forty-five minutes after MDMA administration she said:
“My legs are a little heavy and my chest is a little hot, not a bad thing, I’m not nervous anymore. I feel warm and fuzzy I’m not stressed at all.” At the one hour point, her SUD

[119] SUDs are usually between 0 and 100. The patient obviously invented her own scale.

was 0 (actually, she reported it as “minus 15”). Colors are bright, I feel warm inside, there’s lots of energy… My thoughts are coming fast. I need some direction. Love, I’m seeing blocks to it.” The therapists suggested she focus her attention back inside. After a few minutes she said, “I just heard, ‘You’re the greatest!’… I see the link between the derealization and the rape.” She talked briefly about the rape and became aware of anger, self-blame, and feeling alone, and then said, “There has been desperation under the numbness. I feel protected now, I finally feel loved and protected. (Tears) It’s good to have someone who cares.” She went on to talk some more about the rape in this session with realizations about how experiences in childhood had made her vulnerable. She spent much of the session appreciating being able to really feel, for the first time, how much love and safety there was in her marriage. In the follow-up sessions she said, “Now I have a map of the battlefield. I think next time I’ll be able to go deeper processing the trauma,” which she did. (Mithoefer, 2013a, p.33f)

*About the therapeutic alliance:*

Participant: “It sucks to just live. Y’all are really a godsend. It is so nice to have someone who understands. For so long it’s been take this pill, take that pill. The night that I was raped, the first thing that popped into my mind was ‘they are not going to believe me because of the T-shirt I was wearing.’ I really thought nobody would believe me. And here you are. Just throughout the years, everyone said take this and take that. Nobody’s really bothered to dig down to the symptoms and help me figure out what’s causing this.” (Mithoefer, 2013a, p.36)

*About regained competence:*

“I have respect for my emotions now (rather than fear of them). What’s most comforting is knowing now I can handle difficult feelings without being overwhelmed. I realize feeling the fear and anger is not nearly as big a deal as I thought it would be.” (Mithoefer, 2013a, p.57)

*Shame during the later part of the session:*

> "Now that the medicine has worn off I sometimes feel guilty for saying the things I did about my parents not being emotionally available. I know it wasn't about blame, but there's still that judging voice that says we don't talk about any of this." (Mithoefer, 2013b, p.12)

*About validation during the later part of the session:*

> Therapist: "You know, today you've faced and talked about a lot of difficult experiences in ways you haven't been able to before. It's really important to your healing process that you did, it's definitely a good thing, and it's also really understandable that there would be some second thoughts or judgments about it as the medicine wears off. This is common for people doing this work, and part of our role is to help you process these thoughts and feelings too, and respect that there are parts of you that may not trust the validity of the experience yet, it's all part of the process. How do you see it? Was it a genuine experience or just a drug experience that wasn't really valid or real."
> Participant: "No, it was a real experience. It was my own experience, the drug made it possible, but it was my experience." (Mithoefer, 2013a, p.42)

*Validation and integration:*

> "I had never before felt what I felt today in terms of loving connection. I'm not sure I can reach it again without MDMA but I'm not without hope that it's possible. Maybe it's like having an aerial map so now I know there's a trail." (Mithoefer, 2013b, p.13)

*During the aftermath of a transformative session:*

> "Last night I had a clear sense that I got where I needed to get. What was missing has been found. What I needed, I've gotten. I don't feel like I need to do it again. I think there are still other issues in my life that I can work on with less intense methods." (Mithoefer, 2013a, p.57)

> "It wasn't an easy experience but it was so worth it. It was a very spiritual experience, very expansive. I feel a sense of calm and stability now." (Mithoefer, 2013b, p.13)

*About adaptation into everyday life:*

> "I got a glimpse of more of what I'm capable of growing into…I'm motivated to keep practicing openness until it gets more developed." (Mithoefer, 2013b, p.12)

*Integration; learning new ways in dealing with oneself:*

> "I realize I'm not trying to break through anything. It has to be softly opening. With the medicine nothing felt forced. I know I'm going to have to feel the feelings and there's still fear that the grief will be overwhelming, and I know feelings are unpredictable and the currents can be swirly, but yesterday when I put my toe in it felt so wonderful to feel. I remember every detail, it's a pristine, pristine image." (Mithoefer, 2013b, p.13)

*Realizing the essence of PTSD:*

> "Without the study I don't think I could have ever dug down deep, I was so afraid of the fear." (Mithoefer, 2013b, p.12)

The following paragraphs consist of *written* comments from the long-term follow-up questionnaire (17-74 months after the initial trial):

> "It's been such a long time now that I find it difficult to remember all that's happened - up and down – since the study. I am positive that I felt/experienced a lot of benefit soon after the study and at some point began to notice that the effects seemed to fade. I still feel like night-time is, in general, much better. I may not always sleep better, but I have fewer fears, hear fewer sounds, have fewer racing thoughts. I am in general, less hyper-vigilant.
> […] I wish that I had overcome the sense of not having a future or not being able to get goals and project a future for myself more. That seems to be something I am neither able to "train" myself to do nor which the MDMA study was sufficient to do."[120] (Mithoefer et al., 2013, supplemental material, p.1)

> "Previous counseling and treatment efforts had shown no measurable improvement in my life. I was stuck in an unhappy place. This study changed all that and gave me the possibility of a different outcome. The journey has been difficult and I remain far from any perceived resolution but the possibility is there. I wish for myself that I could have had intense therapeutic treatment with MDMA for an extended period. I believe that would have been very helpful. But, if not me, then I hope those who come after will have the benefit of MDMA therapy. I am grateful for chance to participate in the study. It has given me hope. Thank you." (Mithoefer et al., 2013, supplemental material, p.1f)

> "I feel that I would improve even more with another treatment in a year or two. Please consider me for this if I would be allowed in another study." (Mithoefer et al., 2013, supplemental material, p.2)

[120] The statement is presumably by one of the patients who relapsed.

“The study was so great for me but one of the toughest things I have ever done. I hope what I’ve done will be able to help others.” (Mithoefer et al., 2013, supplemental material, p.4)

“The quality of my life has improved significantly as a result of my participation in this study. I have a much better understanding of my PTSD symptoms and feel that they have improved. I gained an insight into who I am and what I need out of life. ... I have gained tools to lead a healthy, productive, and whole life. I am grateful to have had the opportunity to participate in the study.” (Mithoefer et al., 2013, supplemental material, p.5)

“This study has changed my life. I always describe it to people that the traumas that I have lived through were huge but the ... that I buried my feelings and emotions in to deal with the pain, blocked so much feeling both good and bad. I was always too frightened to look below the surface. To say that moving through it was going to help was laughable to me. Why would I go to hell in order to heal? The MDMA and the support allowed me to pull off the wounds? And I don’t know how to explain it but my spirit or soul knew how and what and how fast or slow I needed to see my pain. It was beautiful really and not frightening. I believe that was greatly helped by the Dr. and his wife who stayed by my side and were a rock and a safe place. I feel it is critical that those who are leading the study know how very important it is and serious it is that they be there in every way possible. PTSD does not make trusting easy, and safety allows one to be open, and being open allows you to let someone in to help you heal. This study saved my life. I will not have the ... down life I was leading and I know I am better that ...and not only am I feeling my life, my trauma does not define me. My trauma makes me a beautiful part of the universe…. Whole and not broken, valuable and not less-than because of my pain. Thank you.” (Mithoefer et al., 2013, supplemental material, p.5)

“This therapy (MDMA) made it possible for me to live. I would recommend it to anyone with PTSD.” (Mithoefer et al., 2013, supplemental material, p.5)

“MDMA is a valuable therapeutic tool and must be re-legalized for use in psychotherapy immediately” (Mithoefer et al., 2013, supplemental material, p.4f)

## Curriculum Vitae

Felix Schuldt

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*Education:*

| | |
|---|---|
| 2003 | Abitur; Albert-Schweitzer-Gymnasium Neckarsulm |
| 2004-2005 | Studies of aerospace engineering at University of Stuttgart |
| 2007-2015 | Studies of psychology at University of Vienna; focus on clinical and medical psychology |

*Experience:*

| | |
|---|---|
| 2014 | Training in MDMA-assisted psychotherapy with Annie and Michael Mithoefer |
| 2013-2015 | Research activities at Medical University Heidelberg |
| 2012 | Internship at 'checkit!' (Suchthilfe Wien gGmbH); drug checking, prevention, counselling |
| 2005-2007 | Elite-A Cross-Country mountain bike rider and trainer |

*Languages:*

| | |
|---|---|
| German | native |
| English | fluent |
| French | basic |

*Publication:*

Jungaberle, H., & Schuldt, F. (2014). Abschied von der Homogenität – Eine Interaktions-Typologie von Jugendlichen in der Prävention des Missbrauchs von Alkohol und anderen Drogen. rausch - Wiener Zeitschrift für Suchttherapie, 1.