c:PsychotherapyMDMAPsychobiologyPerspective

Book Chapter for Philip Murphy's textbook

MDMA assisted psychotherapy - a psychobiological analysis and critique.

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Running head: MDMA psychotherapeutic potential

Introductory preamble.

Can taking the stimulant drug MDMA help to resolve clinical distress? The aim of this article is to critically evaluate this proposal from a psychobiological perspective. MDMA is a methamphetamine derivative with powerful stimulant properties. An acute dose can intensify many mood states, and make individuals feel more empathic and loving, although negative feelings can also be heightened. This has led some psychotherapists to employ this drug as a facilitator for psychotherapy. Positive findings have been reported, although negative outcomes have also occurred (Greer and Tolbert, 1986). From a neuropharmacological perspective, clinical medications such as antipsychotics and antidepressants are taken chronically, in order to correct a neurotransmitter deficiency which is thought to underlie the clinical syndrome. This is not the model which underlies MDMA assisted psychotherapy (Riedlinger and Riedlinger, 1994). Here an acute dose of the drug is used once or twice in on-drug therapy sessions, and these are embedded in a longer series (typically 12) of non-drug therapy sessions. Psychotherapists label MDMA an 'entactogen' which allows the person to get in contact with their 'true self'. Under this state the psychotherapist may be able to help the person resolve their problems; hence it has also been described as insight therapy (Doblin, 2002).

This approach to therapy raises a number of psychobiological concerns, and this chapter will examine many of these practical and theoretical issues. MDMA is neurochemically diverse drug which affects several different neurotransmitter systems (McDowell and Kleber, 1994), hence it can generate a wide range of psychological changes (Parrott, 2013a,b; McCann and Ricaurte, 2014; White, 2014). It has powerful sympathomimetic effects which can generate strong feelings of euphoria in many individuals, and they may facilitate the therapeutic process (Doblin, 2002; Mithoefer et al, 2011). However this CNS stimulation can also intensify negative feelings, and these may make the drug problematic for some individuals (Parrott, 2002; Reid et al, 2007). Indeed acute abreactions have been described by psychotherapists in some of their clients, following MDMA (Greer and Tolbert, 1986). This is because the release of negative feelings and cognitions may be difficult for the individual and their therapist to handle. Another issue is the post-MDMA recovery period, when decreases in functional serotonin can lead to low moods, such as feelings of anger or

depression (Curran and Travill, 1997; Parrott and Lasky, 1998). This may be a particular issue for clients with psychiatric problems such as anxiety or depression. Indeed the psychotherapists Greer and Tolbert (1986) warned against the use of MDMA for clients with psychiatric problems. Nevertheless, recent trials have found that MDMA can speed the psychotherapeutic process, although some of the clinical indicators have shown minimal or inconsistent changes (Bouso et al, 2008; Mithoefer et al, 2011; Oehen et al, 2013). Furthermore they have found some clinical benefits with placebo-treated clients, suggesting that psychotherapy alone can be effective. This also raises questions over the core notion of 'treatment resistance' (Doblin, 2002).

The structure of this chapter is as follows. Firstly a theoretical rationale for the use of MDMA will be presented. Next there will be an historical overview of the early years of MDMA-assisted psychotherapy pre-1986, when it was scheduled as a Class A drug. The next section will undertake a review of the psychobiology of MDMA, focusing on its diverse mood effects, while also covering other psychobiological functions (Parrott, 2013a). The post-MDMA period of neurochemical recovery will then be outlined, and the potential implications for clients debated. This will be followed by an overview of recent clinical trails into MDMA-assisted psychotherapy (Mithoefer et al, 2011; Oehen et al, 2013). The next section will consider potentially safer drug alternatives, such as oxytocin and d-cycloserine (McGregor et al, 2008; De Cline et al, 2013). The final section will present an overview of the psychobiological perspective, and the many practical and theoretical concerns it raises.

Theoretical rationale for the psychotherapeutic use of MDMA

The first detailed report on the use of MDMA by psychotherapists was the seminal paper by psychotherapists Greer and Tolbert (1986). Their research was stimulated by the work of Alexander Shulgin, who noted that the subjective effects of MDMA could be very positive, and suggested to psychotherapist colleagues in California that they should use it for drug-assisted psychotherapy (Shulgin, 1986). A number of informal trials were conducted (Greer and Tolbert, 1986; Nichols 1986; Adamson and Metzner, 1988). Their underlying psychoanalytic focus was reflected in the terminology they developed. They proposed that MDMA was a new type of psychoactive drug which they called an 'entactogen', since it allowed the person to develop closer contact with their 'true self' (Nichols, 1986). This raises an intriguing psychobiological question - what is the true self ? This leads to the corollary question - what is the untrue self ? For the psychobiologist, brain activity is ever changing, and this is reflected in our fluctuating moods and cognitions. For the psychopharmacologist, psychoactive drugs can affect brain activity in many different ways. For instance some psychoactive drugs can generate intense feelings of fear; so could this temporary state be described as the 'true self'? For the psychobiologist, the self is broadly stable over time, with internal homeostatic feedback mechanisms organized around the HPA axis (Parrott et al, 2014). Yet the 'self' is also ever-fluctuating - as it continually develops and adapts to a multitude of external and internal influences. Hence notions such as 'true self' or 'untrue self' have little utility for the psychobiologist or psychopharmacologist. Indeed they have little utility for modern psychology in general, and its simpler focus on 'the self'. These psychoanalytic concepts are also antithetical to modern clinical therapies such as cognitive-behavioural therapy. Here self-evaluation and problem solving are core tenets for personal development.

Returning to the psychoanalytic notion of MDMA as an 'entactogen', this concept was central for the Californian psychotherapists, since it allowed them to propose that MDMA should be clinically useful following just a single drug administration (Greer and Tolbert, 1986), although in later reports it was suggested that 2 or 3 sessions might be necessary (Doblin, 2002). Even later, when this was ineffective, they employed 5 sessions (Oenhen et al, 2013; see later). However the core notion was that once you had perceived your 'true

self', then this realization would remain with you forever. Hence their usage of MDMA was also termed 'insight therapy'. Doblin (2002) suggested that because of these unique pharmacodynamic properties, a minimal number of sessions on MDMA would be required, due to the insights it could generate: 'Ideally, this benefit would require only from one to three drug sessions to produce significant, measurable, and long-lasting clinical progress'. They emphasized that MDMA was a practical aid to facilitate psychotherapy, and should not be conceptualized as chemical pharmacotherapy, as exemplified by traditional antipsychotic or antidepressant medications (Doblin, 2002; Greer and Tolbert, 1986). Riedlinger and Riedlinger (1994) noted that the purpose of MDMA was to 'Enhance the normal psychotherapeutic process rather than serving a maintenance role as chemotherapeutic agent'.

Grinspoon and Bakalar (1986) similarly stated that it was a 'Misunderstanding to consider psychedelic drug therapy as a form of chemotherapy, which must be regarded in the same way as prescribing lithium or phenothiazines'. They further noted: 'The claims of psychedelic drug therapy are subject to the same doubts as those of psychodynamic and other forms of psychotherapy. The mixture of mystical and transcendental claims with therapeutic ones in another aspect of psychedelic drug therapy troubling to our culture'. This quotation was cited in one of my earlier reviews (Parrott, 2007), and it illustrates a fundamental difference between traditional pharmacotherapy (viz: chronic usage of antipsychotic or antidepressant medications), and the totally different approach of psychotherapists (viz: minimal usage of an 'entactogen' to enhance self-awareness). In Parrott (2007) it was further noted that: 'Psychotherapists seem to seek higher-level integrative changes, but these are more intangible. Metzner (1998) stated that with MDMA assisted psychotherapy: 'The drug is used to amplify and intensify the processes of internal self-analysis and self-understanding'. To summarize, there seems to be a fundamental difference in theoretical models between psychoanalysts and psychobiologists. Hence the main aim of this article is to present a detailed psychobiological analysis of the processes thought to underlie MDMA-assisted psychotherapy

In terms of therapeutic mechanisms, Doblin (2002) suggested that painful or troubling memories would be released by MDMA, and that these could then be actively resolved

with the assistance of a trained psychotherapist. Doblin (2002) further proposed that the on-MDMA session should be embedded in a series of non-drug therapy sessions, and this embedded model has been closely followed in all recent studies (Bouso et al, 2008; Mithoefer et al, 2011; Oehen et al, 2013). Greer and Tolbert (1990) offered a similar psychoanalytic explanation for how MDMA might work. They noted that adult problems were due to deep-seated problems from childhood, and that MDMA facilitated access to these repressed emotions. Then the psychotherapist would help the client to reformulate these negative memories in a more positive way. Hence under MDMA, the client could: 'Reassess any aspect of their lives and relationships that they chose, from the broader perspective of security and love'. These psychoanalytic explanatory models raise important questions for the psychobiologist. For instance, if MDMA stimulates the release of troubling cognitive material, might this simply lead to heightened distress? Suppose the client and psychotherapist were not able to reformulate the troubling emergent material in a positive way, this could be therapeutically counterproductive. Especially since it has been proposed that benefits will occur within a single session (Doblin, 2002). Might adverse effects also occur within a single session? Another psychobiological issue is the post-MDMA rebound period. Holland (2001) proposed that: 'MDMA increases the ratio of love to fear'. Yet post-MDMA there is period of low moods and negative cognitions, due to neurotransmitter depletion (Curran and Travill, 1997; Parrott and Lasky, 1998; Parrott et al, 2008). Hence the period of recovery period might be being potentially damaging. To develop Holland's quotation - the post-MDMA period may decrease the ratio of love to fear.

Historical introduction: findings from the early 1980s.

Greer and Tolbert (1986) administered oral doses of either 75mg. or 150mg. MDMA to 29 volunteers in California. Their full report on this study remains invaluable today, since it provides a detailed overview of both the positive and negative experiences of their clients. The drug was manufactured by Alexander Shulgin and tested for purity. Higher doses were given to the heavier people, while the initial dose was sometimes followed 3-4 hours later by a small booster dose. One elderly volunteer was given two sessions of higher doses (200mg, also 350mg), since she had not responded to the standard dose, but this led to severe abreactions which are summarised below. Most of the 29 volunteers had no clinical

diagnosis, and were taking part in the study to get 'insight' into themselves, for curiosity, or other reasons. However nine participants met DSM-lll criteria for a formal psychiatric disorder, such as post-abortion anxiety over sex, depressed mood, or dysthymia. Several other therapeutic studies from this time have also been reported, although they tend to be far less detailed in their descriptions. Adamson and Metzner (1988) utilized MDMA in group psychotherapy sessions, where therapy was seen to occur in the context of a group ritual, with sacramental and religious overtones. Other published reports include Riedlinger and Riedlinger (1994), Holland (2001), Metzner and Adamson (2001), and Naranjo (2001).

These studies from the early 1980s generated a number of positive findings. Many of the experiences under the influence of MDMA were very positive and pleasant, and were often seen as 'life affirming'. Hence many of the participants stated that they felt happier in themselves, and emotionally closer to other people. There were also reports of greater confidence, feelings of security, and more open communication with friends or partners (Greer and Tolbert, 1986). Other positive reactions included heightened sensuality, greater sense of touch, and enhanced sensory awareness. Self-concepts could also be improved, as illustrated by reflective comments such as - 'I felt so good about myself'. Physical warmth was also reported with one participant feeling pleasantly warm (Grinspoon and Bakalar, 1986). Some of these personal experiences were framed in religious or spiritual terms: 'I now feel and know that I am the eyes, ears, feelings of the spirit' (Naranjo, 2001). The majority of these positive subjective experiences occurred when the participants were under the influence of MDMA. However there were also reports that they were more enduring (Grinspoon and Bakalar, 1986; Adamson and Metzner, 1988). Hence there were descriptions of improved understanding and better interpersonal relationships, sometimes for several days afterwards, while occasionally they were reported to continue for weeks or even years. Greer and Tolbert (1986) noted that the duration of these post session effects was highly variable, although the average duration was one week.

Greer and Tolbert (1986) noted that 'Every subject experienced some benefits from MDMA during his/her session'. However they further noted that all 29 subjects also reported 'some undesirable experiences during or after their sessions'. The negative acute effects included jaw clenching, feelings of nausea, muscular aches, increases in heart rate

and blood pressure (note: these final two aspects was measured in just two participants, with pronounced cardiac stimulation occurring in both of the tested volunteers). Negative emotional reactions were noted by 16 participants, with on-drug feelings of tension or anxiety, or feeling lonely/fearful for a brief period, especially during the earlier stages. The post-MDMA period sometimes led feelings of depression, anger, flattened affect, or emotional vulnerability. A few participants noted cognitive issues, such as a racing mind, too much going-on, mental confusion, and negative self-talk for five to seven days afterwards.

One elderly client did not respond to the normal dose, and so she was given higher dose sessions. Unfortunately she developed some very strong abreactions to these high does of MDMA: 'The side effects she reported during sessions were nausea, small amount of vomiting, jaw tension, ataxia, urinary urgency, blurred vision, sweating, brief short-term memory loss, and brief distortion in depth perception with a brief hallucination. During the evening after the sessions, she experienced loss of appetite, a little vomiting, less taste for alcohol, a strong body odour, blurred vision, urinary urgency, a mild hearing impairment, difficulty opening her jaws wide, insomnia and the biting of her cheek during sleep. Her jaw opening difficulty continued for several days, along with two days of fatigue and hoarseness, one day of feeling uncertain on her feet and a brief visual illusion the second night'. In terms of other enduring deficits, two other clients experienced abreactions which lasted for a few weeks or months afterwards; they were summarised in the earlier review (Parrott, 2007): 'Greer and Tolbert (1986) described two clinical abreactions to MDMA, in their volunteers undergoing psychotherapy. One of their participants had experienced disabling symptoms of anxiety a few years earlier. At the time of the MDMA-assisted therapy session he did not fulfill DSM-lll criteria for a psychiatric diagnosis, but during the session he became afraid that he would become overwhelmed by unwanted emotions, and complained of post-session anxiety for an (undefined) period afterwards. Another patient developed appetite and eating problems for an extended period (weeks/months) post-therapy. These experiences led Greer and Tolbert (1986) to warn against using MDMA in vulnerable individuals: 'There is an indication that MDMA may predispose people to a recurrence of previous psychological disabilities'.

Psychobiological profile of MDMA.

MDMA was rescheduled as an illicit drug in 1986, due to the emerging evidence that it was neurotoxic to laboratory animals (Ricaurte et al, 1985; Stone et al, 1987). This concern was well founded, since subsequent research has confirmed that the repeated usage of MDMA can be damaging to the serotonergic system in humans (McCann et al, 1998, 2008; Reneman et al, 2006; Kish et al, 2010; Di Iorio et al, 2012; Benningfield and Cowan, 2013; Parrott, 2013b). Clinical studies ceased around 1986, but have commenced again in recent years (Bouso et al, 2008; Mithoefer et al, 2011; Oehen et al, 2013). Before covering these latter psychotherapy investigations, it will be useful to describe the neurochemical profile of MDMA, along with its physiological and psychological effects in humans. It is important to understand its diverse neuropsychobiological effects. An acute dose of MDMA will increase activation across in several neurotransmitter pathways, most particularly serotonin, but also dopamine, noradrenaline, and others (Green et al, 2003). This can lead to acute changes in many different psychobiological functions (Parrott, 2001; 2006; 2012b; Baylen and Rosenberg, 2006; Dumont and Verkes, 2006). It has powerful effects on the human nervous system, with cardiac stimulation, and a range of acute hormonal changes (Dumont and Verkes, 2006; Parrott, 2009, in press). Its mood effects can be complex, and it can adversely affect some cognitive skills while leaving others intact. MDMA can alter various measures of brain activity, with many of these effects changing over repeated usage (Kish et al, 2010; Parrott, 2013a,b). For MDMA to be used for clinical purposes, a thorough understanding of these multiple psychobiological effects is necessary.

In relation to mood, a common misperception is that MDMA is simply a powerful euphoriant. Yet while feelings of elation and pleasure generally predominate, its mood effects are far more diverse. The first comprehensive mood investigation was undertaken by Vollenweider's group, where 74 drug-naïve participants were given single doses of MDMA (mean 108mg), in three placebo-controlled double-blind studies (Liechti et al, 2001). Unipolar mood scales were administered, and 30 of the 33 self-rating scales generated significant mood increases. Every positive mood state was boosted, where 'item based analysis revealed that subjects were mainly happier, more relaxed, carefree, open, sociable and talkative'. Note the key word 'mainly', since significant increases in a range of negative

mood scales were also found. Hence there were significant increases in self-ratings for apprehension-anxiety, depression, dazed state, visual hallucinations, and altered perceptions. The paradoxical nature of these psychological changes was indicted by significant increases in both extraversion and introversion! It should be emphasized that these complex mood findings developed in a 'calm and comfortable laboratory environment' (Liechti et al, 2001). Hence a moderate dose of MDMA can intensify a wide range of mood states, alter various cognitions, and induce visual hallucinations, in a quiet laboratory environment.

Later double blind laboratory studies have confirmed that acute MDMA can engender a wide range of mood state changes (Bedi et al 2010; Parrott et al 2011a; Kirkpatrick et al, 2012). This mixture of mood changes has also been found in the subjective reports of recreational Ecstasy/MDMA users (Davison and Parrott, 1997). Again positive moods predominate, with Cohen (1998) reporting one quotation 'I felt very much in love with everyone around'… while a participant in Parrott (2010) noted 'Buzzing, love everyone, giggly'. However negative reports have also been noted in recreational users, as in: 'I felt like I was surrounded by water and drowning. It must have been panic' (Cohen, 1998). Some party goers also experience hallucinogenic effects: 'I thought a plastic fish was swimming on the spot out of water' (Parrott, 2010).

Two important influences on the mood states released by MDMA are setting and expectancy. The psychotherapists Greer and Tolbert (1990) emphasized that it was important to establish a positive mental set beforehand, to make sure there were positive expectations about what the therapy sessions might achieve. They further suggested that the establishment of positive mental set and expectancies was more important than the actual drug experience, since they perceived 'the effects of MDMA as secondary to the effects of the therapeutic ritual' (Greer and Tolbert, 1990). Setting and expectancy are also important for recreational Ecstasy/MDMA users, who typically take it with like-minded friends. One recreational user interviewed by Cohen (1998) commented that: 'It is not the type of drug to do alone… be comfortable with the people you are with'. Setting and expectancy are also important for group therapy under MDMA, with Metzner and Adamson (2001) offering formal guidelines for the 'Sacramental use of empathogenic substances'. These guidelines included sections on the establishment of a supportive setting, and how to engender positive expectancies within

the group. Bouso (2001) similarly emphasized that a supportive setting and positive expectancies were crucial for clients with post traumatic stress disorder, since the psychological material released by MDMA could be troublesome for the client to handle.

Post-MDMA: neurochemical recovery and distress.

One key issue for the psychobiologist is the period of post-MDMA neurochemical recovery. As noted earlier, the main proposal is that an acute dose of MDMA will facilitate psychotherapy. However the period of drug-activation lasts just a few hours, even when the initial dose is followed by a secondary booster dose (Greer and Tolbert, 1986; Doblin, 2002; Mithoefer et al, 2011; Oehen et al, 2013). In overall terms, the neuropsychobiological activation will last for around 6-8 hours. Afterwards there will be a period of neurochemical depletion, when low moods and feelings of depression can develop (Curran and Travill, 1997; Parrott and Lasky, 1998; Liechti et al, 2001; Parrott et al 2008; Parrott and Young, 2014). Other psychobiological deficits reported during the recovery period, can include brooding, bad dreams, reduced appetite, heightened sensitivity to pain, poorer memory, and feelings of paranoia (Turner et al, 1999; Liechti et al, 2001; O'Regan and Clow, 2004; Parrott et al, 2011b; Parrott and Young, 2014). In some of these studies the dosage levels were not reported, although in several they were. Parrott and Lasky (1998) reported that their novice recreational users had taken a mean of 1.45 MDMA tablets, while the regular users reported a mean of 1.80 MDMA tablets (estimated dosages of 105mg and 135mg respectively). In Liechti et al (2001) the mean dosage was 103mg, with a range of 70mg – 120mg MDMA. These dosage levels were similar to those employed with MDMA-assisted psychotherapy; hence similar types of adverse effect may be expected in some clients.

Another important practical problem is increased feelings of anger, which can be accompanied by behavioural aggression. Curran et al (2004) found a significant increase in feelings of depression and aggression, four days after taking Ecstasy/MDMA. Furthermore, on a laboratory task there was a significant increase in behavioral aggression. In an American paper entitled Hug Drug or Thug Drug, Reid et al (2007) documented numerous cases of

MDMA induced aggression in recreational users. While in a psychiatric report, Rugani et al (2012) found that patients with psychosis, who had also taken recreational MDMA, demonstrated higher levels of aggression and violence than equivalent patients who had not taken it. These psychiatrists noted that: 'Psychosis with a high level of aggressiveness and violence constitutes an important 'side-effect' that surely runs counter to the expected entactogenic actions of Ecstasy'. Post-MDMA recovery problems were also noted by Greer and Tolbert (1986), where short term problems (under a week) included depression, anxiety, fatigue and insomnia, while longer term problems (over a week) included alterations in appetite, and anxiety/panic attacks. To summarize, acute MDMA is followed by a period of neurochemical recovery, when many different psychobiological indices of wellbeing are impaired (Table 2). The practical concern is that this period can lead to enhanced psychiatric distress, especially in susceptible individuals.

One counter-intuitive aspect of MDMA-assisted therapy is the need to exclude individuals with a prior psychiatric condition. The main proponent for MDMA–assisted therapy, Doblin (2002) stated that: 'MDMA assisted psychotherapy should initially be explored not in patients whose psychiatric symptoms originated with biological imbalances with possible genetic components… but rather in patients who need some assistance in process difficult emotions that have a deep seated component of fear and/or anxiety. Two of the main categories of patient who fit this description are people suffering from Post Traumatic Stress Disorder (PTSD), and people facing terminal illness'. Greer and Tolbert (1986) also warned against using MDMA in psychiatrically vulnerable individuals: 'There is an indication that MDMA may predispose people to a recurrence of previous psychological disabilities'. Hence the most recent studies all exclude individuals with a prior psychiatric diagnosis (Bouso et al, 2008; Mithoefer et al, 2011; Oehen et al, 2013). Another important issue is that with reactive clinical disorders such as PTSD, display a natural tendency for recovery over time; hence the folklore adage 'time is a great healer'. Tucker et al (2003) compared sertraline, citalopram, and placebo, and found reductions in PTSD symptoms following both active treatments *and* placebo.

Recent studies into MDMA-assisted psychotherapy.

Rick Doblin is a key figure for empirical research into MDMA-assisted psychotherapy (Doblin, 2002), since his MAPS organization has sponsored all three recent trials. Bouso et al (2008) undertook MDMA-assisted psychotherapy with six women suffering from chronic PTSD secondary to sexual assault. They administered low doses of MDMA or placebo. Two clients were given 0mg, three were given 50mg, while a single person was given 75mg. It was found that these dosage levels were physiologically safe. Clinical changes were measured using the Severity of Symptoms Scale for Post-Traumatic Stress Disorder, and some other measures. In overall terms, each condition led to some slight benefits, with minimal gains after placebo, slightly more gains after 50mg, and somewhat more in the single person given 75mg. However the small effcts and minimal sample sizes limit any formal conclusions.

Mithoefer et al (2011) empirically investigated MDMA-assisted psychotherapy in 20 clients with long-standing post-traumatic stress disorder. The main causes of PTSD were childhood sexual abuse or sexual assault in adulthood. It should be noted that 45% of the clients had taken MDMA previously (mean lifetime usage 9 occasions). Twelve patients were given two MDMA assisted therapy sessions (125mg followed by a supplementary dose of 62.5mg), embedded in series of ten drug-free therapy sessions. Eight patients were given two placebo-assisted sessions, embedded within a parallel series of drug-free therapy sessions. Hence the majority of the twelve psychotherapy sessions were drug-free. Drug administration was double-blind, although 19 of the 20 clients correctly guessed their drug condition, while the psychotherapists were correct in every 20 instance. Hence although the study was designed as double-blind, in practical terms this was not achievable, due to the clear psychophysiological effects of MDMA. It may be noted that Oehen et al (2013, see below), employed an active-placebo design, and partially resolved this issue.

Clinical symptoms were assessed using the Clinician Administered Post-Traumatic Stress Disorder scale (CAPS), and it was found that: ‘PTSD symptoms, as measured by CAPS, improved over time in both groups (time, $p<0.0005$), but the MDMA group show significantly greater improvement (time x group interaction, $p=0.015$). Paired t-tests showed that the MDMA group had significantly lower PTSD scores after all treatment sessions than the placebo group’ (see Figure 3 in Mithoefer et al, 2011). Somewhat surprisingly the ANOVA group effect was not described, so presumably it was non-

significant, otherwise it would have been presented. A second measure of clinical wellbeing was the Impact of Events Scale Revised (IES-R), a self-report measure devised to measure the DSM-IV criteria for PTSD. The IES-R scale showed a very similar pattern of findings to CAPS, with a significant time/session effect, a significant group by time interaction, while the ANOVA group effect was not documented (again presumably it was non-significant). It was noted that the IES-R scores 'improved over time in both groups, but the MDMA showed significantly greater improvement' (see Figure 4 in Mithoefer et al, 2011). The absence of ANOVA group effect findings from the journal report is surprising; it does suggest that the placebo and MDMA conditions were not statistically different.

Each client also completed the Symptom Checklist 90-Revised, although these findings were unfortunately not described in the journal report (Mithoefer et al, 2011). Around this time, at the 'Breaking Convention' Conference on MDMA-assisted psychotherapy, held at the University of Kent UK, I enquired about these SCL 90-R findings, and Rick Doblin kindly arranged for them to be sent to me. He reported that they had not found any significant effects on the overall SCL 90-R scale, whereas there were changes in the anxiety and depression subscales. Their emails noted a number of non-significant and significant findings, which will now be briefly summarised. The ANOVA revealed a significant time effect for the SCL-90 Anxiety subscale (over the four sessions, $p<0.001$), the time x drug condition interaction was non-significant ($p=0.367$), while drug condition was also non-significant. In terms of group means, the MDMA condition SCL-90 Anxiety score reduced from 51.0 at baseline to 39.7 at 2 months, whereas the placebo group score reduced from 51.4 at baseline to 45.1 at 2 months. Hence there was a significant reduction in anxiety with psychotherapy for all clients, irrespective of the drug condition. Clinical improvements had occurred under both MDMA and placebo.

With the SCL-90 Depression scale there was a significant ANOVA time effect ($p<0.001$), a significant time by drug group interaction ($p<0.05$), and a non-significant drug group effect. The pattern of changes over time scores differed between the two groups. In the MDMA group depression scores reduced from 52.4 at baseline, to 40.9 after session 1, 40.8 after session two, and 38.5 at 2-month follow-up. The placebo SCL-90 Depression scores changed more gradually from 49.5 at baseline, to 50.3 after session 1, then 46.5 after

session 2, and 42.1 after 2 months. Doblin and his team debated these differing patterns of change over time in their email: 'What actually seems to happen is that the MDMA scores remain low, while placebo depression scores approach MDMA participant values over each successive assessment'. Hence there was a significant overall reduction in depression with all clients following psychotherapy, *irrespective of the drug condition.* The pattern of change was different for the two drug conditions, with a rapid reduction following MDMA, and a more gradual reduction following placebo. These findings provide empirical support for a quotation from Holland (2001), who noted that 'Good psychotherapy often works, but it takes years. MDMA markedly accelerates and intensifies the process'. See also Riedlinger and Montagne (2001), who suggested that one session of MDMA-assisted therapy was equivalent to five months of normal weekly therapy.

Mithoefer et al (2011) noted that the acute physiological effects of MDMA included a significant increase in blood pressure, pulse rate and body temperature, peaking around 2 hours post-drug, and returning to baseline by the end of the session. Side effects documented in the paper were 'spontaneously reported'. It would have been far better if side-effects had been collected systematically from every participant, using standard self-rating scales. This procedure should certainly be undertaken in any future trails, since relying on 'spontaneous reports' can seriously underestimate any drug effects (whether positive or negative). Their spontaneous reports of negative effects included 'jaw tightness, nausea, feeling cold, dizziness, loss of appetite, and impaired balance'. There was also one adverse clinical outcome, with one client dropping out 'because she required resumption of medication for relapse of depression 42 days after her one MDMA-assisted session'.

In overall terms, there are three main clinical findings from Mithoefer et al (2011). Firstly psychotherapy was clinically effective, with significant improvements in PTSD symptoms over the series of 12 psychotherapy sessions. Secondly, clinical improvements were found both in the MDMA group, and in the placebo group. Thirdly, the patterns of change over time differed between the two groups, with significant ANOVA group by session interaction factors. With MDMA-assisted therapy, a rapid gain was found after the first session, but after this the symptoms largely stabilized. With placebo assisted therapy, there was a slow and gradual improvement in clinical symptoms over time. In the Abstract of the

study, it was noted that: ‘The rate of clinical response was 10/12 (83%) in the active treatment group, versus 2/8 (25%) in the placebo treated group’. This conclusion is often cited for the study, since it suggests a dramatic benefit for MDMA over placebo. However the full findings are far more subtle, and show closer similarities between MDMA and placebo.

Mithoefer et al (2013) undertook a follow-up of participants from the above study, at time intervals ranging from 17 to 74 months. They found that mean CAPS scores at the end of their first study, were maintained at similar group mean levels during the follow-up. Sixteen participants provided full data, with fourteen showing stable clinical gains, while two of the sixteen experienced a clinical relapse. It should be noted that everyone in this follow-up sample had been treated with MDMA-assisted therapy. This was because at the end of the first study, every participant in the placebo condition was offered MDMA-assisted therapy sessions, and 7 of the 8 opted for this. The other participant declined since she had benefited strongly from placebo-assisted therapy.

Oehen et al (2013) undertook a similar trial to Mithoefer, assessing 12 patients with long-standing PTSD (10 female, 2 male). Eight were given a full dosage of MDMA of 125mg, followed by a supplementary dose of 62.5mg; the other four were given an ‘active placebo’ of 25mg MDMA followed by a supplementary dose of 12.5mg. This design was partially successful in hiding the drug conditions, since the active placebo condition generated slight psychophysiological effects. Unlike Mithoefer et al (2011), they administered three MDMA-assisted psychotherapy session, although this was embedded in a total of twelve psychotherapy sessions (nine being non-drug). Clinical changes were monitored using the CAPS scale in a German translation. The clinical findings showed a very different pattern of changes from those reported by Mithoefer et al (2011). After the first two sessions of MDMA-assisted psychotherapy, the group mean CAPS scores remained almost unchanged. They reduced slightly from 66.4 to 63.0 in the high dose MDMA condition, and showed a similar minimal reduction from 63.4 to 60.0 in the active placebo condition. Basically the clinical effects of the first two sessions of MDMA-assisted therapy were negligible (see Figure 2 in Oehen et al, 2013). Then following a third session of MDMA-assisted therapy, the active placebo group deteriorated slightly (to 66.5), whereas the high dosage group

showed a reduction (to 50.8). The other clinical measure was the Post-traumatic Diagnostic Scale, and on this measure the active placebo group started lower and increased after treatment (23.5 increasing to 30.8), whereas the full dose group started higher and reduced after treatment (30.8 reducing to 21.4). This crossover generated a significant ANOVA group x time interaction ($p=0.014$). It is unclear why the two clinical scales in Oehen et al, (2013) showed such different patterns of change over time. Another complicating issue was that the authors modified the protocol in the middle of the study. They noted: 'After a preliminary analysis of data showed an insufficient clinical response to the experimental treatment in several full dose subjects, an amendment to the protocol was obtained, allowing for two additional sessions of MDMA assisted therapy for any subject deemed to show insufficient response'. The new doses that the MDMA-unresponsive clients were given were higher - at 225mg MDMA per session (150mg followed by a supplementary dose of 75mg). The authors then also gave full doses of MDMA to those initially allocated to the placebo group! These post-hoc changes to the design, made it difficult to compare longer-term effects of MDMA versus placebo.

There are a number of other methodological limitations to these small pilot studies, and these were acknowledged in the published reports (Mithoefer et al, 2011; Oehen et al, 2013; Parrott, 2014). However it remains unclear why Mithoefer et al (2011) found such a large reduction in CAPS scores after just one session of MDMA-assisted therapy, whereas Oehen et al (2013) found very minimal changes in CAPS scores after the first two sessions of MDMA assisted therapy. The dosage levels of MDMA were identical in both studies. The basic study designs and overall duration of 12 therapy sessions were also identical. The clients all had long standing chronic PTSD, with an average duration of 19-20 years in both studies. The main difference was the control condition. So was the active placebo effective in blinding the assessors – and did that somehow influence their assessments? Another potential factor might be different patterns of psychotherapy. Did they differ in the levels of expectancy generated within their respective clients, or in some other more intangible aspects of psychotherapeutic interventions?

Potentially safer drugs for PTSD-therapy.

De Kline et al (2013) undertook an empirical review of four different drugs which had been used for drug-assisted psychotherapy of PTSD. Given its relevance and importance, a previous summary of their review (Parrott, 2014a), will now be outlined: 'De Kline et al (2013) noted that several co-drugs had been shown to be effective in the treatment of Post Traumatic Stress Disorder (PTSD), and that they were safer to use than MDMA. Several forms of psychological therapy had been shown to be effective, with 'prolonged exposure therapy' being the 'first line of treatment recommended in guidelines worldwide'. They noted that not all PTSD clients benefited from psychological therapy alone, and described four drugs which had been investigated as potential pharmacological enhancers: d-cycloserine, MDMA, hydrocortisone, and propanolol. Their review concluded that all four agents had some supporting evidence for enhanced efficacy, although the data was very limited. They discussed adverse side effects, and noted that three of the four drugs were safe and well tolerated, although MDMA was not in that category. De Kline et al (2013) concluded: 'Reflecting on the clinical utility of these cognitive enhancers, with the exception of MDMA, they seem to be safe and well tolerated'. The potential and/or documented problems with MDMA, were outlined on pages 7-8 of de Kline et al (2013). Their MDMA subsection ended with the following interesting suggestion: 'The alternative of oxytocin enhancement may have better clinical utility, considering that it is easily administered e.g. as a nasal spray and produces little adverse effects'. Several authors have suggested that oxytocin may be effective for drug-assisted therapy (McGregor et al, 2008; Olff et al, 2010). To summarise, oxytocin might provide a more focused co-drug for PTSD therapy. Future trials of MDMA-assisted therapy should include active control conditions, using drugs with known efficacy for PTSD.

Finally, if MDMA is providing brief period of heightened moods, there are far safer *non-drug* ways of achieving positive feelings, which could also be more enduring. They include relaxation therapy, yoga, reading groups, film debating societies, voluntary social work, and regular physical exercise. These life-affirming activities can be very helpful for increasing physical, mental and psychosocial health. In terms of future research, MDMA might be empirically compared with periods of yoga or mind-fullness training. [In passing, less television might also be beneficial, since prolonged television watching can foster passivity, inactivity, and depression]. Hence psychotherapists may need to broaden their

battery of practical tools for helping their clients. The core aims should be to develop positive expectancies, improved self-concepts, and dynamic life skills.

- Table 1 near here -

Psychobiological conclusions and concerns

This chapter comprises my fourth review of MDMA assisted psychotherapy. Parrott (2007) comprised a broad overview of the whole notion, and it was undertaken because previous articles had all been written by those closely involved with the venture (Doblin, 2002). Hence a more independent and dispassionate review was clearly needed. The second review (Parrott, 2014a), was based on an invited paper at the Breaking Convention Conference at Kent University in the UK (see earlier). This second paper covered the more recent empirical findings, and expanded on my many theoretical and practical concerns. The third article (Parrott, 2014b) comprised a reply to Doblin et al's (2014) critique of my empirical overview of the neurobiological effects of MDMA, and its use within psychotherapy (Parrott, 2013b). In the current chapter paper I have focused on some core psychobiological issues. My concerns are summarized in Table 1, where I have attempted to distill both potential benefits, and potential problems.

In psychobiological terms, MDMA is a very powerful CNS stimulant drug, and its acute administration can be metabolically stressing for the organism, leading to biochemical overactivation, acute and chronic stress (Darvish and Gudelsky, 2005; Hegadoren et al, 1998; Parrott, 2002, 2013a.b; Kish et al, 2010; Benningfield and Cohen, 2013; Parrott et al, 2014). Its psychophysiological effects include heating up the body and brain, impaired thermal control, leading to feeling hot or cold (Freedman et al, 2005; Parrott, 2011; Mithoefer et al, 2011; Parrott and Young, 2015). Its acute somatic effects can include nausea, jaw clenching, teeth grinding, headache, increased heartbeat, muscle aches, fatigue, dizziness, vertigo, dry mouth, sweating, numbness, unsteadiness, tics and tremors, restlessness and agitation (Baylen and Rosenberg, 2006). Some of these somatic effects have been noted with clients in MDMA-assisted therapy; although they are typically mild

(Mithoefer et al, 2011), they can be more severe when the dosage is high (Greer and Tolbert, 1986).

Acute MDMA can also induce hormonal changes, such as increases in cortisol and oxytocin (Gerra et al, 2001; Wolff et al, 2006; McGregor et al, 2008). Indeed the acute increase in oxytocin my partially underlie some of its positive mood effects (McGregor et al, 2008; Dumont et al, 2009; Parrott, in press). The increase in cortisol may also contribute to its activating effects, and lead to disturbances in homeostatic balance (Parrott, 2009; Wetherell and Montgomery, 2013; Frokjaer et al, 2013). Cortisol dysregulation may also underlie the sleep problems reported by some clients after MDMA-assisted therapy (McCann and Ricaurte, 2014). The essential point is that MDMA is a powerful and neurochemically complex drug, and its usage can lead to a range of acute and chronic psychobiological problems (McCann et al, 1998; 2004; Parrott, 2001, 2002, 2006, 2009, 2013a,b; Kish et al, 2010; Taurah et al, 2013; White, 2014; many others). Given that MDMA has a powerful neuroactive profile, if it is to be used for clinical purposes it is important to ascertain its safety. Furthermore, it must not be clinically damaging. Yet psychotherapists find that MDMA can generate negative moods and release troublesome cognitions (Greer and Tolbert, 1986; Bouso, 2001). Hence one potential problem is that some individuals may develop negative experiences which are clinically distressing (Table 1). The emergent psychological material may be susceptible to set and expectancy, and while some psychotherapists may be able to establish supportive conditions, this cannot be guaranteed, and abreactions can occur even with experienced psychotherapists (Greer and Tolbert, 1986).

An opposite problem is when clients really like the drug (Table 1). In a previous review it was noted that vulnerable clients might start taking illicit supplies, and develop the classic serotonergic problems of repeating users. This prediction was confirmed by an external reviewer of one of my previous articles (Parrott, 2014a); this professional drug abuse counselor from San Francisco wrote that: ‘I have seen patients with previously diagnosed depression become worse after an MDMA session for another reason – it worked TOO well, acutely, made the feel great or at least normal, and then the crash make them feel all the worse than before. Could it be posited that this is a risk for both exacerbated depression

and drug abuse – “I want more of that”.’ This may be a minimal issue for middle-aged clients with chronic PTSD. However it could be an important concern for younger clients. Many young soldiers develop PTSD after distressing war experiences, and they may particularly at risk, since illicit supplies of MDMA are readily obtainable at clubs and music festivals.

Another issue is the period of neurochemical recovery following MDMA, since this may lead to heightened clinical distress, especially in vulnerable individuals (Curran and Travill, 1997; Parrott and Lasky, 1998). Indeed it is widely recognized that it is inadvisable to administer any CNS stimulant drug to psychiatrically vulnerable individuals (Table 1). Stimulant-drug abreactions are widely recognized with recreational users of CNS stimulants, including amphetamine, cocaine, nicotine and methamphetamine (Dittrich et al, 1994; Parrott, 1999, 2015; Parrott and Murphy, 2012). Psychiatric abreactions in vulnerable individuals can also occur with MDMA (Greer and Tolbert, 1986). This explains why all recent studies of MDMA–assisted therapy have employed psychiatric exclusion criteria (Bouso et al, 2008; Mithoefer et al, 2011, 2013; Oehen et al, 2013). Yet this important exclusion has not reached public consciousness; in their undergraduate essays, my university students repeatedly miss-state that MDMA is used to treat psychiatric disorders.

Dosage escalation is another practical issue, since MDMA is being used over more sessions, and at increasing dosage levels ! The first proposals for MDMA-assisted therapy were that it would be beneficial after just a single session (Greer and Tolbert, 1986). Later it was suggested that while one session would generally be sufficient, an additional one or two sessions might be necessary (Doblin, 2002). Oehen et al (2013) found that several of their eight clients did not show any benefits from three sessions of MDMA assisted-therapy, so they were given two more sessions - at even higher dosage levels ! (see previous section). See also the case of severe adverse effects following high doses of MDMA, in the elderly client who had not responded to the standard dose (Greer and Tolbert, 1986); the adverse consequences were both severe and lasted for several days. Given that dosage escalation occurred in these strictly controlled trials, it would become commonplace if MDMA were made available to all psychotherapists.

This leads to the next problem (Table 1), namely that many of the advocates for MDMA-assisted therapy do not seem to recognize that MDMA is a powerful stimulant drug with numerous adverse properties. As a general pharmacodynamic principle, the more powerful the drug, the more damage it can cause. This pattern holds for all CNS stimulants (Parrott, 2015), and MDMA is one of most powerful of the stimulant drugs. Hence it is not surprising that MDMA displays a wide range of damaging effects, both acutely and chronically. Recreational users have died from single doses of MDMA, while others develop the serotonin syndrome or acute hyponatraemia (Parrott, 2002; Hall and Henry 2006; Halpern et al, 2011; Van Dijken et al, 2013). The adverse psychobiological effects of regular Ecstasy/MDMA usage are numerous, and although they can be quite subtle in light users (Parrott, 2013b), they can be far more damaging in heavy users (Janssen, 1997; Soar et al, 2004; Reay et al, 2006; Taurah et al, 2013; Downey et al, 2014). They can include deficits in memory, thinking and reasoning, emotional intelligence, patterns of brain activity, serotonergic dysfunction, reduced immunocompetence, increased pain perception, altered appetite, disrupted homeostasis, neurohormonal changes, heightened stress or depression, and many others. The list of psychobiological problems has lengthened as empirical knowledge has increased (Parrott, 2000, 2001, 2006, 2009; 2012a,b, 2013a,b). My most recent review (Parrott, 2013a) was criticized by Doblin et al (2013), and I recommend the reader to read both their critique, and my reply (Parrott, 2014b).

The final issue is public perception. Articles about MDMA-assisted therapy in the press have often stated that it is being used by therapists to resolve clinical distress. The readers then believe that since the drug is medically approved, it must be safe for them to take recreationally. This issue of social perception was debated in earlier articles (Parrott, 2013, 2014a,b), since it generates very inaccurate concepts and beliefs in young people: ‘One of my main concerns about MDMA-assisted psychotherapy, is the very misleading message being sent to young people. Around ten years ago, one of our participants stated that he had been against taking MDMA, until he read an article in a scientific journal stating that MDMA was being licensed for use in psychotherapy. That meant MDMA must be safe – and so he started using it recreationally. When assessed later in our neurocognitive study, he showed the typical memory deficits, and other associated problems. How many other

young people have perceived this misleading message – and decided to use MDMA recreationally as a result? Every year my university students inform me that since MDMA has been approved for therapy, it must be safe for them to use (Parrott, 2014a). The inaccuracy of this belief can be illustrated by the empirical findings of Taurah et al (2013). They found that current and former Ecstasy/MDMA polydrug users displayed various psychological deficits, and that former users displayed minimal recovery despite several years of abstinence. Taurah et al (2013) concluded that: 'Given this record of impaired memory and clinically significant levels depression, impulsiveness, and sleep disturbance, the prognosis for the current generation of ecstasy users is a major cause for concern'. To summarize, MDMA is not a safe drug. The advocates for MDMA-assisted psychotherapy see MDMA as a magic bullet with 'entactogenic' properties. Yet in psychobiological terms, MDMA is just another damaging CNS stimulant (Parrott, 2015). The initial effects of MDMA can be very pleasant, especially when taken with a positive mental set. However acutely it can be damaging, and its repeated usage can lead to many neuropsychobiological deficits (Table 1). There are far too many health concerns for MDMA to be accepted as a safe drug for human consumption.

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Table 1. MDMA- assisted psychotherapy: overview of potential benefits and deficits

Potential benefits.

Positive moods, cognitions, and social bonds: euphoric feelings and elated moods; interpersonal feelings enhanced; greater interpersonal trust; bond with therapist facilitated.

Negative cognitions restructured: troublesome events from the past re-evaluated with the assistance of a trained psychotherapist.

Reduced fear response: feelings of fear reduced; enhanced coping with past events; emotional anesthesia.

Setting and expectancy: psychological factors may be more important than the actual drug.

Safer drugs with potential benefits: psychotherapy may be facilitated with other/safer drugs (see text).

Potential deficits.

Negative moods and cognitions: enhanced release of negative psychological material, which may lead to acute and chronic distress; increased anxiety or fear.

Post-MDMA neuropsychobiological rebound: neurochemical depletion in the days afterwards; feelings of tiredness, irritability, and tension; mild or severe depression, especially in susceptible individuals.

Stimulant drug abreactions in psychiatrically vulnerable patients: CNS stimulants especially inadvisable for clients with a psychiatric condition; cocaine, amphetamine, methamphetamine provide neurochemical models for psychosis; MDMA can stimulate the release of problematic psychological material and lead to acute and chronic abreactions.

Metabolic overactivation and neuropsychobiological distress: MDMA is an acute metabolic stressor, with a range of potentially adverse psychophysiological and neurobiological effects (details in text).

Drug liking leading to illicit usage: If the client likes the subjective effects of MDMA, they may decide to take it illicitly. Its regular use can then lead to a wide range of neuropsychobiological problems (see text).

Increasing number of MDMA sessions: the original proposal was for one session of MDMA-assisted therapy. This soon increased to three sessions. The latest study employed five MDMA-assisted sessions, with extra sessions for those who had not responded to three MDMA sessions (Oehen et al, 2013).

Dosage escalation: In the above study, the total dosage at the later sessions was increased to 225mg MDMA. In another psychotherapy study, even higher doses of MDMA were given to a client who had not responded positively to a standard dose of MDMA (Greer and Tolbert, 1986); they developed severe adverse side-effects, some of which continued for several days (see text).

Psychobiological damage with MDMA: patterns of brain activity can be altered, and associated psychobiological functions can be damaged by repeated MDMA (see text for details).

Public misperceptions about MDMA: the public misunderstands the core notions of MDMA-assisted psychotherapy; it mistakenly believes that MDMA is safe to take, and can resolve clinical distress.