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REVIEW

The psychotherapeutic potential of MDMA (3,4-methylenedioxymethamphetamine): an evidence-based review

A. C. Parrott

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Abstract
Aims and rationale The purpose of this study was to review whether methylenedioxymethamphetamine (MDMA) has the appropriate pharmacodynamic profile to be a therapeutic agent.
Materials and methods Empirical descriptions of MDMA's subjective effects in humans will be reviewed to evaluate the proposal that MDMA has psychotherapeutic properties. The focus will be published evidence on its functional effects in therapeutic, medical, and other situations.
Results MDMA is a powerful central nervous system (CNS) stimulant which affects several neurotransmitter systems and intensifies a range of psychobiological functions. Its acute mood effects can be very positive and life enhancing, and the affirmative cognitions engendered during MDMA therapy may well endure afterwards. However, MDMA also has a number of potential anti-therapeutic characteristics. Acutely, it can also intensify negative cognitions, and these may similarly endure over time. Psychotherapists have found that setting, intention, and expectancy are crucial for a positive outcome, but these factors cannot be guaranteed. Post-MDMA, there is a period of neurotransmitter recovery when low moods predominate, and these may exacerbate psychiatric distress. The explanations proposed for MDMA-assisted therapy are all psychodynamic, and a neurochemical model needs to be outlined. It has been suggested that enduring therapeutic gains can follow a single session, but again, this lacks a clear psychopharmacological rationale. Finally, diathesis–stress models suggest that psychiatric individuals are more prone to acute and chronic abreactions to CNS stimulants such as MDMA.
Conclusions There are a number of issues which need to be addressed before it can be argued that MDMA might be clinically useful for psychotherapy.

Keywords MDMA · Ecstasy · Serotonin · Stress · PTSD · Trauma · Psychotherapy · Psychiatry

A. C. Parrott (✉)
Department of Psychology, University of Wales Swansea,
Swansea SA2 8PP, Wales, UK
e-mail: a.c.parrott@swansea.ac.uk

Psychotherapy with MDMA: situation prior to 1985

In the first scientific description of MDMA's effects in humans, Shulgin and Nichols (1978) noted that MDMA induced: 'an easily controlled altered state of consciousness with emotional and sensual overtones'. Shulgin (1986) noted that the acute subjective effects of this ring-substituted amphetamine derivative could be very positive and life-affirming, and suggested to Leo Zeff and other psychotherapist friends that it might prove useful in therapy (Holland 2001a). Initial reports about its efficacy were encouraging, and during the early 1980s, a number of psychotherapists in California were using MDMA as an adjunct for psychotherapy. Nichols (1986) suggested that MDMA or Adam exemplified a new class of compounds, the 'entactogens', which allowed the person to establish deeper contact with their true self (Table 1). Metzner proposed that MDMA and related compounds were 'empathogens', which facilitated interpersonal understanding and feelings of empathy (Metzner and Adamson 2001). At a meeting organized to debate drug-assisted psychotherapy held at the Esalen Institute in California, Greer (1985) estimated that West Coast psychotherapists had used MDMA in more than a thousand therapy sessions. These therapeutic experiences have been described in several

Table 1 MDMA usage for psychotherapy: proposed beneficial effects

Uses	Benefits	References
Entactogenic and empathogenic	Deeper contact with true self; enhanced recognition of the positive aspects of self; stronger bonding with the positive aspects of others	Nichols 1986; Metzner 1998; Mithoefer 2005
Positive moods, cognitions, and beliefs	Euphoric and elated moods; overwhelming feelings of love; interpersonal feelings enhanced; social bonding facilitated; positive enduring cognitive models about the world	Doblin 2002; Parrott 2001; Holland 2001a; Rodgers et al. 2006
Negative emergent material re-evaluated	Troublesome psychological events from the past may emerge into consciousness; this can be re-evaluated with the assistance of a psychotherapist	Doblin 2002; Greer and Tolbert 1990
Reduced fear response	Feelings of fear reduced; this can allow any difficult/negative emergent material to be re-evaluated; this may be related to physical and/or emotional anesthesia	Doblin 2002; Greer and Tolbert 1986
Facilitate client–therapist bonding	Stronger interpersonal bonding; greater feelings of trust; this can facilitate the therapeutic alliance; more rapid therapy with fewer sessions required	Grinspoon and Bakalar 1986; Riedlinger and Montagne 2001

reports (Greer and Tolbert 1986; Adamson and Metzner 1988; Naranjo 2001; Holland 2001b).

The most detailed and comprehensive description was by Greer and Tolbert (1986). Twenty-nine participants, a mixture of personal friends and informal referrals from other psychotherapists, were administered oral doses of 75–150 mg. MDMA followed a few hours later by a smaller dose to prolong the session. Nine of the participants met DSM-III criteria for a psychiatric disorder; these included mixed personality disorder, post-abortion phobia of sexuality, adjustment disorder with depressed mood, and dysthymia. The findings from this important cohort have been described in Greer and Tolbert (1986, 1990, 1998) and elsewhere (Grinspoon and Bakalar 1986; Holland and Greer 2001). The reports are detailed and comprehensive, but more importantly, they cover both the beneficial and more problematic aspects of the endeavor. The other reports from this period are generally less detailed and mainly focus on the positive aspects. Adamson and Metzner (1988) described the use of MDMA or 'Adam' in group psychotherapy sessions, modeled on the approaches of traditional societies where: 'When curing or therapy takes place, it happens in the context of a ritual shared by the group'. They emphasized the contextual, sacramental, and religious elements to the healing process, with case study descriptions (see below). The experiences of this group are also described in Metzner and Adamson (2001) and Naranjo (2001). A third group of reports covered the therapeutic use of MDMA for depression (Riedlinger and Montagne 2001; Riedlinger and Riedlinger 1994), although essentially theoretical, they contain descriptions of personal experiences. The fourth groups of studies were by Holland (2001a,b) who debated the use of MDMA for therapy in general and for schizophrenia in particular.

Many of the experiences under MDMA were extremely positive. Hence, the following personal descriptions: 'Primarily an intense warmth and security about myself and other people'... 'MDMA breaks down inhibitions about communication'... 'It surprised me that I felt so good about myself ...for having been so deeply into my real self, crying my heart out, and how healthy it felt to know that I had really been there for those feelings' (Grinspoon and Bakalar 1986). One recreational user with a diagnosis of schizophrenia reported: 'The paranoia that I was experiencing was temporarily halted and replaced with an immense sense of love, compassion, intimacy and closeness' (Holland 2001b). These reports noted that every sensory modality could be boosted by acute MDMA. Increased interpersonal sensitivity, heightened sensuality, and sense of touch were commonly noted, whereas another reported feeling: 'pleasantly warm, which was unusual for her' (Grinspoon and Bakalar 1986). Sometimes, the sensory changes are imbued with spiritual awareness: 'I now feel and know that I am the eyes, ears, feelings of the spirit. I feel so safe, so protected. The Holy Spirit is myself' (Naranjo 2001). One Yoga practitioner found that MDMA facilitated the flow of physical 'kundalini' energy—the creative source of energy originating from the base of the spine: 'My body danced and leaped with the kundalini energy. I just let it dance and loved it' (Metzner and Adamson 2001). Cognitions were often enhanced, with reports of expanded mental perspective, improved self-examination, and stronger self-beliefs: 'During the course of a single Adam session, I experienced a deep natural healing within myself.... For the first time in my life, I can feel myself consciously and lovingly aware of the body in which I live' (Adamson and Metzner 1988).

Several reports noted that these positive changes had endured over time. Improved understanding, increased empathy, and more life-affirming attitudes, remained evident for weeks or months after the MDMA-assisted therapy sessions had ended: 'I expanded my boundaries, grew in dimensions, and in general feel I have more awareness of what it is to be alive'... 'I got rid of a lot of negative material I carried around with me forever...this has

resulted in more energy, a greater feeling of freedom and strength, deeper joy, less pain' (Grinspoon and Bakalar 1986). Others reported more positive interpersonal understandings and a greater facility for experiencing love in everyday life: 'I am able to perceive, receive, and respond to love in a much more open way than I did a few weeks ago (Adamson and Metzner 1988). These beneficial changes covered both self-beliefs and wider perspectives about the world: 'It had a lasting effect on my own self-view and worldview. In some sense, it gives me a role model for what sort of personality I would like to achieve' (Holland 2001b). Wider psychobiological benefits were also reported: 'In the two weeks that have followed, I have observed the following behavioral changes. I choose lighter healthful foods and no longer desire heavy, fatty foods. There has been a definite increase in the grace with which I move, and an instinctive desire for water and a marked increase in daily fluid intake' (Metzner and Adamson 2001). Another client who was suffering from breast cancer reported the beneficial effects of stronger imagery when she imagined the cells in her body moving towards healing (Metzner and Adamson 2001).

Although many these personal experiences are impressive and persuasive (Table 1), the methodological limitations of the findings should be noted. In Greer and Tolbert (1986) and all the other reports from this period, there was no control group. Hence, any post-therapy changes due to MDMA could not be distinguished from the effects of the psychotherapy alone. The findings were also confounded with set and expectancy and the natural processes of recovery over time. Standardized clinical rating scales were not employed so that there was no quantitative indication of baseline distress levels nor of how psychiatric symptoms had changed post-therapy. The positive experiences were also accompanied by a number of more negative reactions, both during the MDMA-assisted therapy sessions and in the days and weeks afterwards (see later for examples). Hence, the overall effects of MDMA-assisted psychotherapy, the balance of beneficial versus detrimental consequences, cannot be gauged (Parrott et al. 2004). Finally, most of the participants in Greer and Tolbert (1986) did not have a formal psychiatric disorder, being friends and acquaintances. The clinical utility of the other reports from this period is even more limited, as they mainly comprise quotations from selected case studies (Adamson and Metzner 1988; Naranjo 2001; Holland 2001b). Despite its methodological limitations, Greer and Tolbert (1986) therefore remains the most useful of all the reports from this period. Their detailed analysis allowed them to conclude that taking MDMA was physically safe, that its side-effects were not serious, and it displayed clear potential as pharmacological adjunct for insight-orientated psychotherapy (Greer and Tolbert 1986, 1990).

MDMA assisted psychotherapy: the current situation

MDMA and the other ring-substituted amphetamine derivatives were categorized as illegal around 1985–1986, and this precluded further research into its therapeutic potential for a number of years (Doblin 2002; Greer and Tolbert 1990; Hegadoren et al. 1998; Holland 2001a,b; McCann et al. 2000; Metzner and Adamson 2001; Parrott 2001). For much of this period, the Multidisciplinary Association for Psychedelic Studies (MAPS) has been applying for permission to undertake a program of sophisticated investigations into the psychotherapeutic potential of MDMA. This program of studies was outlined in Doblin (2002) where it was stated: 'In terms of therapeutic potential, MDMA is remarkably effective, gentle yet profound... MDMA rarely interferes with cognitive functioning or perception and usually produces a warm, emotionally grounded feeling with a sense of self-acceptance, and a reduction of fear and defensiveness'. Comparisons were made with other psychedelic drugs such as lysergic acid diethylamide (LSD), but Doblin noted that they had greater potential for abreactions. The core proposal was for MDMA to be used by specially trained psychotherapists in a series of studies into the treatment of post-traumatic stress disorder (PTSD). Mithoefer (2005) has also described these plans in detail and outlined a number of core predictions. Pilot studies have been initiated (Doblin 2002), but they have been delayed by subsequent setbacks (Chack 2004). Other research programs for MDMA-assisted psychotherapy have been planned in Spain, Switzerland, and Israel, but again, they have been delayed or halted for medical or legal reasons (Bouso 2001; Caudevilla, personal communication, 2006). Updates on the progress of these initial studies are posted on the MAPS website (Doblin, personal communication, 2006).

Aims of the current review

One of the underlying arguments of Doblin (2002) was that MDMA should be evaluated in a similar way to any other psychoactive drug, irrespective of its legal status and recreational 'misuse'. Hence, its psychotherapeutic potential needs to be assessed in a purely scientific manner. The aim of the current paper was to provide a scientific and dispassionate overview of MDMA's psychotherapeutic potential. Before 1987, there was little empirical evidence on the effects of MDMA in humans, but now, there is a far more extensive database (Baylen and Rosenberg 2006; Dumont and Verkes 2006; Hegadoren et al. 1998; Parrott 2001, 2006). One of the main aims of this paper was to review all aspects of MDMA which might relate to therapy and identify issues which will need to be addressed in

future therapeutic research. The following topics will be addressed. Firstly, the acute subjective effects of Ecstasy/MDMA will be reviewed to assess how they might influence psychotherapy. Secondly, the recovery period will be considered, as the after-effects may adversely affect well-being. Thirdly, it has been suggested that therapeutic gain can be achieved with just a single MDMA-assisted session (Greer and Tolbert 1986, 1990; Doblin 2002), so this notion of a 'magic bullet' will be evaluated. The duration of any experiential and/or therapeutic changes and the contributory role of non-drug factors such as intention, setting, and expectancy will also be debated. The neurochemical rationale for using MDMA as a pharmacotherapeutic agent will be discussed. Most of the explanatory models have been psychotherapeutic rather than neurochemical, so both areas need to be critically examined. Next, the type of psychiatric disorders suitable for MDMA-assisted therapy will be debated in the context of diathesis–stress models of well-being. The core focus will be on whether psychiatrically susceptible individuals may be more prone to abreactions to CNS stimulant drugs such as MDMA. Finally, somatic aspects, drug safety, and related non-functional topics will be briefly noted.

Acute MDMA: experiential effects

MDMA administration induces neurotransmitter activation across several neural pathways including serotonin, dopamine, noradrenaline, and others (Green et al. 2003; Hegadoren et al. 1998). This broad spectrum of neurochemical activation can lead to an acute changes in many different psychobiological functions (Dumont and Verkes 2006; Baylen and Rosenberg 2006). The subjective mood effects have been assessed in several studies, although most have involved small sample sizes, and they have generally employed bipolar mood scales. The most comprehensive mood data have emerged from three related studies by Vollenweider's group where the same basic methodology was employed throughout (Vollenweider et al. 1998; Gamma et al. 2000; Liechti and Vollenweider 2000). In total, 74 drug-naïve participants were administered single oral doses of MDMA (mean 108±16 mg) in a series of placebo-controlled double-blind studies. The environment was a controlled medical setting, and the overall findings were summarized in Liechti et al. (2001). Standardized self-rating mood questionnaires were administered, and crucially, they employed unipolar rather than bipolar scales. In 30 of the 33 mood scales, there was a significant mood increase under MDMA. There was a significant increase in *every* positive mood scale, including 'basic positive mood', 'self-confidence', and 'emotional excitation'. Several of these positive changes would facilitate psychotherapy, with significant increases in 'sensitivity', 'thoughtfulness–contemplativeness', and 'facilitated imagination' (Table 1). However, most of the negative mood states were *also* significantly boosted by MDMA, with increased levels of 'apprehensiveness–anxiety', 'dazed state', and 'depressiveness'. Several of these more problematic scales overlapped with symptoms of psychiatric distress. So that under MDMA, there were significant increases in 'fear of loss of thought control', 'depersonalization', 'visual (pseudo)-hallucinations', and 'manic like experiences' (Table 2 here; Table 1 in Liechti et al. 2001).

This broad spectrum of mood changes in the clinic (Liechti et al. 2001) is paralleled by the reports of recreational ecstasy/MDMA users. Positive euphoric experiences predominate, with Cohen (1998) noting the following subjective descriptions by American clubbers. 'I felt very much in love with everyone around'... 'I felt happy and free and glad to be alive'... 'It is a benevolent feeling of connecting with people, the community, the world, and your inner self'. Occasionally, the subjective experiences on Ecstasy/MDMA can be negative (Cohen 1998; Davison and Parrott 1997) as evidenced by the following subjective descriptions: 'Out of control. Too much energy'... 'I had a bad experience. I felt like I was surrounded by water and drowning. It must have been panic' (Cohen 1998). Some recreational users have described a mixture of positive and negative elements, whereas others feel skeptical about the nature of the drug-induced experience: 'Is the feeling of happiness real or is it just from a pill. Am I really this happy, appreciative and loving, I'll tell you tomorrow' (Cohen 1998). A similar mixture of positive and negative experiences occurs in the therapeutic setting. In Greer and Tolberts (1986) investigation of acute MDMA administration in 29 volunteers, 18 described positive changes in mood state, including euphoria, energy, sereneness, and relaxation. However, 16 of the participants reported less desirable emotional symptoms such as anxiety, and there were also reports of adverse cognitive/mental experiences such as 'confusion' and 'too much going on in the mind'.

In acute terms, MDMA is therefore a general stimulant and activator, increasing emotional intensity across a broad range of mood states (Tables 1 and 2). The explicit combination of positive and negative experiences is illustrated by the following client undergoing MDMA-assisted therapy: 'I briefly tried to fantasize about catastrophes like an earthquake. I did not feel anxious or threatened' (Grinspoon and Bakalar 1986). The general activation of contrasting psychological states is also evident in the clinical/medical situation. For instance, self-rated extraversion and introversion were *both* significantly enhanced in Liechti et al. (2001). Recreational users can feel more friendly and outward-going, but also more reflective and introspective, during the same MDMA

Table 2 MDMA usage for psychotherapy: potential detrimental effects

Uses	Disadvantages	References
Negative moods and cognitions	Release of positive and negative psychological material both boosted by MDMA; the negative material may cause acute psychological distress	Cohen 1998; Greer and Tolbert 1986; Grinspoon and Bakalar 1986; Parrott 2001
Post-MDMA rebound phenomena	Neurochemical depletion in the days afterwards may lead to tiredness, irritability, depression, and wider psychobiological distress; individuals with psychiatric predisposition factors may be more susceptible to these rebound/recovery problems	Curran et al. 2004; Greer and Tolbert 1986; Parrott and Lasky 1998
Stimulant drug abreactions in psychiatric patients	The use of CNS stimulants is inadvisable in many psychiatric conditions since adverse symptoms may be increased; amphetamine provides a neurochemical model for psychosis; MDMA may stimulate the release of problematic psychiatric material; stimulant drug abreactions can occur in various situations, including MDMA-assisted psychotherapy	Caton et al. 2000; Dittrich 1994; Greer and Tolbert 1986; Parrott 2006
Acute metabolic/ psychobiological distress	MDMA is an acute metabolic stressor; MDMA has a wide range of potentially adverse psychobiological effects; the incidence and severity of these effects is unpredictable; rebound phenomena are not limited to moods and cognitions, but can include a wide range of psychobiological functions	Baylen and Rosenberg 2006: Darvesh and Gudelsky 2005; Parrott 2002, 2007a; Lock et al. 2006
Adverse chronic psychobiological sequelae	A range of adverse psychobiological changes can occur post-MDMA; their overall frequency is associated with lifetime usage, although untoward events can occur after minimal usage	Gerra et al. 2001; Greer and Tolbert 1986; Hegadoren et al. 1998; Rodgers et al. 2006

experience. In a similar way, self-ratings for happiness and depressiveness were both significantly increased under MDMA (see earlier). Psychotherapists have suggested that the drug-induced emergence of problematic thoughts and feelings into consciousness will facilitate their resolution during psychotherapy. Bouso (2001) proposed that during therapy for post-traumatic stress disorder, the use of MDMA would allow the client: 'To get in touch with painful emotions as well as happy ones' and that this would facilitate their treatment by making: 'Access to these intense emotions more comfortable, effective, and easier'. However, this raising into consciousness of deep-seated problematic events from the past is potentially troublesome. The client and therapist may find the emergent material difficult to cope with, and the concern is that the client may suffer from increased distress, either during the session or afterwards (see later for some examples).

Setting and expectancy

Greer and Tolbert (1990) stated that it was important to establish the appropriate mental set to generate a positive therapeutic outcome. They outlined a number of practical recommendations for the preparation of both therapist and client. The sharing of past experiences and discussion about what the sessions might achieve was seen as crucial, as: 'This mutual sharing established a context of...collaboration, intimacy, confidentiality, and trust'. They also stated that mental set was more crucial than the actual drug for a successful clinical outcome: 'We viewed the effects of MDMA as secondary to the effects of the therapeutic ritual'. ... 'The quality of the relationship between patient and therapist was...more important even than the dose taken' (Greer and Tolbert 1990). Setting and expectancy are also important in other situations of MDMA usage. Recreational users often state that it is crucial to build up a positive expectancy before taking MDMA and to be with like-minded friends when under its influence (Parrott et al. 2004). One American recreational user noted: 'It is not the type of drug to do alone...it is best to be familiar with and comfortable with the people you are with' (Cohen 1998). Setting and expectancy are also important when MDMA is used in group therapy sessions. In their Guidelines for the Sacramental use of Empathogenic Substances, Metzner and Adamson (2001) included separate sections on preparation and set, setting, and context. They further stated: 'The single most important foundation for beneficial experience is intention or purpose'. Bouso (2001) noted that set, expectancy, and gaining the clients trust and confidence would be especially important in the treatment of post-traumatic stress disorder, as the emergent material could be potentially troublesome. Finally, Metzner and Adamson (2001) recommended that all therapists should have taken MDMA themselves to understand the on-drug experiences of their clients.

Post-MDMA recovery and long-term consequences

The period of mood activation induced by acute MDMA is comparatively brief, typically around 5–6 h. Afterwards, there is a period of neurochemical depletion when feelings of anhedonia, lethargy, and depression may develop (Curran and Travill 1997; Curran et al. 2004; Gahlinger 2004; Green et al. 2003; Greer and Tolbert 1986; Liechti et al. 2001; Lock et al. 2006; Parrott 2001; Parrott and Lasky 1998). Post-MDMA recovery phenomena were noted in the medical laboratory studies of Liechti et al. (2001). Up to one third of their subjects reported 'slightly depressed mood', including emotional irritability, lack of energy, brooding, and bad dreams. The adverse moods were noted in the days immediately after MDMA, with women tending to report them more frequently than men. Recovery phenomena have also been described in the therapeutic situation. Greer and Tolbert (1986) noted 'All subjects reported some undesirable experiences during or after their sessions. The longest that any of these symptoms persisted was one week, except in two subjects'. The shorter-term (under 1 week) adverse phenomena included depression, anxiety, fatigue, insomnia, muscle aches, and reduced appetite. The longer term changes found in two clients were of altered appetite/eating behavior and increased anxiety/panic attacks (see later).

The post-ecstasy/MDMA recovery period is often called the 'midweek blues' by recreational users. Curran and Travill (1997) noted reduced moods 5 days after taking recreational ecstasy, with several of their participants reporting Beck depression inventory scores within the clinical range. In another prospective study, Parrott and Lasky (1998) found that self-rated sadness and unsociability were significantly increased 2 days after taking Ecstasy/MDMA, but returned to baseline values within a week. Curran et al. (2004) documented a significant increase in self-rated aggression and depression 4 days after taking Ecstasy/MDMA, and again, these values had returned to normal after 7 days. It is not just mood states which are adversely affected. On a behavioral task, Curran et al. (2004) found a significantly greater aggressiveness bias at the mid-week session. O'Regan and Clow (2004) found a significant decrease in pain threshold (i.e., more pain) during the recovery period. Turner et al. (1998) reported that appetite and food intake were significantly reduced for several days after Ecstasy. To summarize, acute MDMA is followed by a period of neurochemical recovery when many different psychobiological indices of well-being are impaired (Table 2). The concern is that this period may lead to enhanced psychiatric distress especially in susceptible individuals.

An important question is whether taking MDMA leads to any longer term changes in well-being. Greer and Tolbert (1986) noted that several of their participants described enduring benefits, with more positive outlooks, feelings of personal strength, and a greater awareness of being alive; examples of these beneficial changes were given in the first section. However, negative changes were also noted, including the recurrence of anxiety symptoms in someone who had previously suffered from clinical anxiety (details later). This mixture of positive and negative outcomes is also evident in recreational Ecstasy/MDMA users. Rodgers et al. (2006) surveyed 157 recreational users about any negative or positive changes they would attribute to ecstasy use. Content analysis revealed several themes. Around 38% of the sample reported an improved outlook on life: 'Became more open minded, happy, friendly, positive about life'. Other beneficial themes, reported by smaller proportions of the sample, were greater understanding of the self and increased sociability. The main negative theme to emerge, reported by 32% of the sample, was psychological problems: 'Depression—anxiety about stupid things—paranoia'. Other negative themes, reported less frequently, included social distress and physical problems such as thermal stress and reduced sex drive. One limitation with all these findings is that their duration was often unclear (Greer and Tolbert 1986; Rodgers et al. 2006). Future research should focus on how long these positive and negative changes endure over time.

Psychodynamic explanations and single session efficacy

Greer and Tolbert (1986) suggested that a single session of MDMA-assisted psychotherapy was often sufficient to generate a successful outcome. Doblin (2002) similarly stated that MDMA's unique profile meant that it could be effective after a single administration, although one or two further MDMA-assisted therapy sessions could sometimes be required: 'Ideally, this benefit would require only from one to three drug sessions to produce significant, measurable, and long-lasting clinical progress'. This suggestion of rapid efficacy is markedly different from other forms of pharmacotherapy where regular chronic dosing is the norm (Julien 2001; Parrott et al. 2004). The main reason given for this rapid efficacy is that MDMA is seen as an aid for psychotherapy rather than acting as a chemotherapeutic agent (Doblin 2002; Greer and Tolbert 1986; Grinspoon and Bakalar 1986; Riedlinger and Riedlinger 1994).

Three psychodynamic models for MDMA-assisted therapy have been proposed (Table 1). Doblin (2002) suggested that MDMA facilitates 'processing difficult emotions that have a deep component of fear and/or anxiety'. Painful memories, which emerge during the MDMA experience, are re-examined with the assistance of the psychotherapist, and this allows the long-standing emotional conflict to be

resolved. Doblin (2002) noted that this could often occur after just a single session. Occasionally, several therapy sessions might be required, but these would involve a mixture of drug-free sessions interspersed with a few more MDMA-assisted sessions. This model relies upon negative-troubling material being released/boosted under MDMA (see earlier). Here, the skilled psychotherapist is seen as essential, as they are needed to guide the resolution of any potentially problematic material. Greer and Tolbert (1990) offered a similar psychodynamic explanation. Adult problems were described as being due to deep-seated childhood experiences and conditioned fear responses. The power of MDMA facilitated access to these long-repressed emotions so that they could be reformulated within a positive emotional framework: 'With the fear removed, a corrective emotional experience could occur.... They could reassess any aspect of their lives and relationships that they chose, from the broader perspective of security and love, rather than from one of vulnerability and fear'. Rapid efficacy was possible because the emotional insights gained during the therapy session could be consolidated into the patients' lives, so providing an enduring resolution. Greer and Tolbert (1990) emphasized that it was crucial that MDMA was used with the explicit intention of learning from the experience: 'Taking MDMA with an intention to learn, with an attitude of acceptance, and in a safely structured setting enabled people to experience their true nature which is essentially loving and forgiving'.

Mithoefer (2005) focused more on the positive acute effects of MDMA, citing Nichols (1986) description of MDMA as an entactogen (Table 1). The acute stimulation of positive moods and cognitions led to one of the core goals of psychotherapy—a feeling of wholeness and integration. This model is consistent with the extensive literature showing that MDMA can induce very positive beliefs and psychosocial cognitions (Cohen 1998; Davison and Parrott 1997; Green et al. 2003; Greer and Tolbert 1986, 1990; Hegadoren et al. 1998; Holland 2001a; Parrott 2001). Holland (2001a) stated that: 'MDMA increases the ratio of love to fear'. Unfortunately, this model also notes that the post-MDMA period will be dominated by low moods and negative cognitions due to rebound neurotransmitter depletion (Curran and Travill 1997; Curran et al. 2004; Green et al. 2003; Parrott 2001, 2006). Hence, the benefits of MDMA should be short-lived, rather than enduring, and the recovery period may well be therapeutically counter-productive. In particular, the post-MDMA period will often *decrease* the ratio of love to fear. Mithoefer (2005) noted these rebound problems, but suggested that: 'Proper preparation and follow-up support will reduce the difficulties participants might have'. Holland (2001a) also suggested that the post-MDMA recovery phase might provide a period for reflection and relaxation when the therapeutic gains could be consolidated.

The third psychodynamic explanation is more general. Grinspoon and Bakalar (1986) suggested that MDMA improved the trust and emotional bonding between client and therapist: 'Many patients report how much more they trust the therapist and how much closer they feel to the therapist after one such session. If, as many believe, the strength of the therapeutic alliance is the best predictor of a good outcome in therapy, this characteristic of MDMA would be of very general usefulness'. Riedlinger and Montagne (2001) noted that MDMA could speed the therapeutic process; they cited one therapist who reported that one session of MDMA-assisted therapy was equivalent to 5 months of normal weekly therapy sessions (Table 1). Holland (2001a) similarly noted: 'Good psychotherapy often works, but it takes years. MDMA markedly accelerates and intensifies the process'. Riedlinger and Riedlinger (1994) commented that the main therapeutic purpose of MDMA: 'Would be to enhance the normal psychotherapeutic process rather than serving a maintenance role as chemotherapeutic agent'.

Neurochemical models

Mithoefers (2005) description of MDMA as an entactogen has a clear neurochemical rationale, as the acute release of serotonin and dopamine can lead to strong feelings of interpersonal empathy (Cohen 1998; Hegadoren et al. 1998; Holland 2001a; Liechti et al. 2001; Nichols 1986; Parrott 2001; Shulgin 1986). Yet, as noted above, this neurochemical explanation also predicts that the benefits of MDMA should be short-lived, rather than enduring, also that its after-effects may be therapeutically counter-productive. The psychodynamic model outlined by Greer and Tolbert (1990) has a more tenuous neurochemical rationale: 'We do not understand how MDMA reduces the experience of feeling threatened...with the barrier of fear removed, a loving and forgiving awareness seems to occur quite naturally and spontaneously'. Greer and Tolbert (1990) suggested that this reduction in fear may reflect a form of emotional anesthesia, as one of their patients had described anesthesia to physical pain while on MDMA. [Note: an acute reduction in pain has also been suggested for psychotherapy under LSD (Kurland et al. 1973)]. Serotonin is involved in pain regulation, and thus, any acute reduction in pain could have a neurochemical basis. The effects of acute MDMA on pain do not seem to have been empirically determined, although O'Regan and Clow (2004) also reported a significant reduction in pain threshold (i.e., greater propensity for physical pain) 3 days after recreational Ecstasy/MDMA.

Doblin (2002) compared MDMA with the selective serotonin reuptake inhibitor sertraline as treatments for post-traumatic stress disorder. Sertraline leads to a chronic

increase in functional serotonin, and this underlies its clinical efficacy for the treatment of PTSD and depression (Davidson 2004; Tucker et al. 2003). Doblin (2002) characterized MDMA as a psychedelic therapeutic (Leary 1969), but did not debate the neurochemical implications of this categorization. According to Doblin (2002), MDMA was fundamentally different from the chemotherapeutic sertraline. In particular, a single dose of MDMA could have enduring beneficial effects so that repeated dosing was not generally necessary. Whereas, sertraline could only offer symptomatic relief, so that repeated dosing was always required. Doblin (2002) noted: 'The hypothesis is that there will not be a return to baseline after the MDMA treatment is over. This is different for sertraline (Zoloft), which offers mostly symptomatic relief with a significant number of subjects relapsing once the use of Zoloft is ended. From a financial perspective, this seems ideal for a pharmaceutical product, as patients have a continued need to purchase the product or the symptoms will return'.

Riedlinger and Riedlinger (1994) suggested that when MDMA was used to treat depression, it would not be acting as a chemotherapeutic but rather to facilitate psychotherapy. Grinspoon and Bakalar (1986) also stated: 'It is 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 noted that: '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 illustrates a fundamental difference in philosophical approach, between medicinal pharmacotherapy, and drug-assisted psychotherapy. The aims of clinical psychopharmacology are relatively easy to measure. Successful outcome for a pharmaceutical drug is symptomatic relief, and clinical improvement is readily measured using standardized questionnaires and rating scales. 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'. If this is indeed the aim of psychotherapy, then assessment devices need to be developed which can measure whether this has been achieved or not. It also raises the core question of whether an enhancement in self-awareness will have any specific clinical or symptomatic benefits.

Psychiatric disorders and MDMA treatment

Doblin (2002) suggested 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 processing 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, 1998) assessed mainly normal volunteers, but their cohort included several clients with predominantly neurotic types of problem. A number of positive responses occurred, which were briefly summarized in the first section. Two clinical abreactions also occurred, but they are summarized later. But although there can be therapeutic benefits with MDMA, the exact nature of these clinical improvements was often unclear. The benefits which have been described are often not specific to any symptoms (Table 1), but seem more to reflect a global induction of positive moods and cognitions. Furthermore, the duration of these post-therapy changes was often unclear; in many individuals, the changes (benefits and deficits) seem to be quite short-lived. Future studies should employ comprehensive clinical ratings to objectively determine the nature of the changes (positive and/or negative) and their duration. Another methodological issue is that reactive disorders such as PTSD typically display a natural tendency for recovery over time, irrespective of the treatment offered. Tucker et al. (2003) found that after 10 weeks, there was a significant reduction in symptoms of PTSD under citalopram, sertraline, *and placebo*. Other PTSD studies have also found significant relief of symptoms under placebo (Davidson 2004). This emphasizes the importance of including a placebo group when evaluating reactive disorders such as PTSD. Indeed, Doblin (2002) and Mithoefer (2005) have emphasized the importance of including placebo conditions when empirically assessing MDMA-assisted psychotherapy.

It has been proposed that MDMA may be useful for the treatment of endogenous psychiatric disorders such as schizophrenia and depression. Riedlinger and Montagne (2001) debated its use for clinical depression: 'Because it is a potent releaser of serotonin into the synapse, and because of its short duration of effect, MDMA seems to be both effective and efficient as a drug for the medical treatment of depression. It works to enhance serotonergic function and mood in matter of hours instead of weeks (as is the case for most prescription antidepressants), and it is effective when administered infrequently, perhaps in weekly or monthly dosing intervals'. No empirical data was presented to support this suggestion, although there were case study descriptions of benefits under MDMA. Later, it was suggested that MDMA might be part useful in the initial treatment of suicidal depression—due to its rapid action. Surprisingly, there was minimal discussion about the potential adverse effects during the neurochemical rebound period. This could be a serious problem in suicidal

depression, as an increase in depressive ideas and suicidal thoughts might occur during the post-MDMA recovery period (Curran et al. 2004; Parrott and Lasky 1998). Hence, MDMA could heighten the risk of suicide afterwards in susceptible individuals.

Holland (2001b) suggested that MDMA might be useful for the treatment of schizophrenia. The main proposal was that it could alleviate the negative symptoms of schizophrenia such as social isolation. This was supported by three case studies of schizophrenics who had self-administered recreational ecstasy/MDMA in social settings and emailed Holland with personal descriptions of euphoric feelings and social integration. The first report noted: 'On MDMA, I found myself more able to talk with almost anyone about almost anything and felt rather freed of most neuroses/psychoses that normally plague me'. The second person reported: 'The paranoia that I was experiencing was temporarily halted and replaced with an immense sense of love, compassion, intimacy and closeness. Please note that MDMA only reduced my paranoia temporarily; the paranoia came back later. But the insight that I gained form the precious few hours of clarity proved to be invaluable'. Similar benefits were described by the third person: 'It has given me freedom from a disease that has plagued me for years, and a bit of that freedom is present even after the drug wears off. I do not think this is a cure for anything, it offers only a new perspective that should be used wisely' (Holland 2001b).

There are several concerns about these proposals. There is no neurochemical rationale for MDMA as a chemotherapeutic agent in either schizophrenia or depression. In particular, any acute mood gains would be followed by subchronic mood decrements. The relief of clinical symptoms was only temporary, and they returned soon after the drug had worn off. This leads to the notion that MDMA would only be beneficial when taken with professional psychotherapy (Holland 2001b; Riedlinger and Montagne 2001). The three case studies in Holland (2001b) were of recreational Ecstasy/MDMA users in social situations, presumably at clubs or dances, without any psychotherapists in attendance (although there may have been some partying psychiatrists; see Liester et al. 1992). However, the main concern is that the boost in dopamine with MDMA could exacerbate the symptoms of schizophrenia in a way similar to amphetamine and other CNS stimulants (Krystal et al. 2005; Stone 1973). This raises the general issue of psychiatric vulnerability.

Psychiatric vulnerability and stimulant drugs

The primary concern here is whether the use of CNS stimulants such as MDMA is particularly inadvisable in individuals with a psychiatric predisposition. The concern is that a pre-existing propensity for distress will increase the likelihood of an acute or chronic drug abreactions. Amphetamine provides a laboratory model for psychosis, as in healthy volunteers, its acute administration induces feelings of hostility and grandiosity, along with other more positive symptoms such as feelings of euphoria (Krystal et al. 2005). 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-III 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'.

The recreational usage of amphetamine and cocaine are each associated with enhanced levels of psychiatric distress (Parrott et al. 2004; Stone 1973). The co-morbidity between psychiatric problems and recreational stimulant use has become an extensive area for applied research. Diagnostic instruments such as the Psychiatric Research Interview for Substance and Mental Disorders have been developed in an attempt to tease out the complex interactions between psychiatric vulnerability factors and psychoactive stimulant usage (Caton et al. 2000). Recreational Ecstasy/MDMA is also associated with enhanced psychiatric distress (Parrott et al. 2000, 2001, 2002; Schifano 2000), although again, it is difficult to distinguish between the many possible causative factors. Some of the Ecstasy/MDMA users who report psychiatric problems have a prior psychiatric history, suggesting that the primary cause of their problems may be pre-dispositional (Huizink et al. 2006). However, other recreational users who develop psychiatric problems do *not* have a prior psychiatric history, supporting a drug-based causation (Soar et al. 2001). Internal and external factors are both important. MacInnes et al. (2001) found that the regular use of MDMA was associated with an increased incidence of depression, but only in certain individuals. They explained their findings using a 'vulnerability model' of depression whereby individuals with prior vulnerability factors were more likely to develop MDMA-related depression. A similar interactive model was utilized by Butler and Montgomery (2004) to describe their findings of greater impulsivity in the heavier MDMA users. They noted that impulsivity was often a personality characteristic of stimulant drug users, with regular Ecstasy/MDMA usage

then intensifying this predisposition. For a fuller discussion of the diathesis–stress model for psychiatric distress and MDMA usage, see Parrott (2006).

Laboratory-based studies have always screened potential volunteers for psychiatric factors, so there are no placebo-controlled clinical data on the effects of MDMA in vulnerable individuals (Parrott 2006). Grob et al. (1996) undertook the first laboratory study of MDMA in humans (experienced recreational users) and screened out anyone with a history of major psychiatric disorder including schizophrenia, major affective disorder, panic disorder, obsessive compulsive disorder, and substance abuse. Vollenweider et al. (1998) undertook the first laboratory administration of MDMA to drug-naïve volunteers and employed even stricter exclusion criteria. These included any history of psychiatric disorder, either in the individual or a first-degree relative, also high scores on the "openness" and "neuroticism" dimensions of the Freiburg personality inventory. Vollenweider et al. (1998) noted that the reason for these exclusions was that individuals with these traits were: 'Particularly liable to prolonged and severe responses to stimulant and hallucinogenic drugs (Dittrich 1994)'.

Somatic and more general aspects

MDMA often has the reputation of being a relatively benign drug (Iversen 2006; Nutt 2006), but in psychophysiological terms, it is a powerful CNS stimulant and metabolic stressor (Darvesh and Gudelsky 2005; Downing 1986; Huether et al. 1997; Parrott 2002, 2006, 2007a,b). Baylen and Rosenberg (2006) listed the following somatic effects of acute MDMA: nausea, jaw clenching, teeth grinding, headache, body temperature changes, accelerated heartbeat, muscle aches, fatigue, dizziness, vertigo, dry mouth, thirst, energy, sweating, numbness, tingling skin, ataxia, unsteadiness, tics, tremors, restlessness, agitation, and nystagmus. Several of these effects are comparatively rare, whereas others are more frequent (Baylen and Rosenberg 2006). Greer and Tolbert (1986) noted some of these somatic changes in their clients, generally to a mild extent. Acute MDMA can also induce a number of hormonal changes, whereas its regular use can lead to enduring hormonal changes (Gerra et al. 2001; Lock et al. 2006; Wolff et al. 2006). These psychobiological effects would need to be considered in any potential medicament (Table 2).

One of the general findings to emerge from this review was the similarity of drug effects emerging from therapeutic, clinical/medical, and recreational situations. Similar patterns occurred in every area considered: the type positive mood gains; the parallel stimulation of negative mood states; the general preponderance of positive acute effects; the general psychophysiological stimulation; the adverse rebound and recovery phenomena; the mixture of beneficial and detrimental longer term sequelae; the contributory influence of non-drug factors such as setting and expectancy; also the interactions with premorbid characteristics including psychiatric disposition. This broad congruence is also consistent with the notion that recreational Ecstasy users are *generally* taking MDMA. Tablet impurity was a serious problem during the mid-1990s, but in recent years, most ecstasy surveys have found high rates of purity (Cole et al. 2002; Parrott 2004a; Lock et al. 2006). Nevertheless, care must still be taken in extrapolating the findings from recreational users, as they take Ecstasy/MDMA in stimulating environments and are often polydrug users (Parrott 2004b, 2006; Scholey et al. 2004). Finally, as in any article about MDMA, the issue of serotonergic neurotoxicity should be noted. This topic is debated at length in the

Table 3 MDMA-assisted psychotherapy: some important questions for future research

MDMA profile	Issues
Neurochemical models	Psychopharmacological models for how MDMA can alleviate clinical distress need to be developed; in psychodynamic models, the neurochemical elements of MDMA's contribution need to be described more fully
Psychotherapeutic models	Does a therapist guide or otherwise contribute to the positive effects; does the therapist provide a safety net for negative or potentially troublesome emergent material; what exactly is the role of the psychotherapeutic contribution; what are the differences between MDMA taken alone, MDMA taken with friends, and MDMA when taken with a therapist?
Single-session efficacy	Is a single session of therapy effective, and if so, for how long; would more sessions facilitate therapy and/or make it more enduring?
Setting and expectancy	How crucial are these factors; can the effects of set, setting, intention, and expectancy, be separated and compared; how do they compare with drug alone?
Nature of clinical benefits	Are there any specific clinical benefits with MDMA; are the primary effects of MDMA more global and integrative and if so, how does this facilitate clinical change?
Nature of deficits	How do predisposition factors relate to the emergent material; is there a relationship between a-priori problems and adverse drug sequelae; which predisposition factors are associated with beneficial and detrimental responses?
Duration of changes	How enduring are the psychological changes post-therapy; do the positive and negative sequelae have a similar time course; can the positive gains be enhanced via prior intentions and optimal expectations?

following articles where the difficulties involved in extrapolating the animal data to humans are noted (Buchert et al. 2006; De la Torre and Farre 2004; Ricaurte et al. 2000; Schifano 2000; Reneman et al. 2006; Quinton and Yamamoto 2006). Neurotoxicity is, however, only of marginal relevance here, as in humans, it is primarily an issue of repeated drug usage (Guillot 2005; Parrott 2001; Reneman et al. 2006; Schifano 2000; Thomasius et al. 2006). Nevertheless, it would be another potentially important factor for any proposed medication.

Conclusions

MDMA is a remarkable drug, with subjective effects that can be extremely positive and life-enhancing. Many recreational users extol its virtues, and it is not surprising that the *Father of Ecstasy*, Alexander Shulgin, suggested that it might prove effective as a psychotherapeutic agent (Saunders 1997; Shulgin 1986). Given its unique profile, it was suggested that MDMA represented a new class of compounds, the entactogens or empathogens, which could enhance the fulfillment of psychological potential (Nichols 1986). The testimonies of psychotherapists who have used MDMA, and the experiences of some of their clients, can be extremely persuasive (Greer and Tolbert 1986; Doblin 2002; Grinspoon and Bakalar 1986; Holland 2001b; Liester et al. 1992). Many review or commentary papers have noted that MDMA may have potential as a psychotherapeutic agent (Dumont and Verkes 2006; Halpern 2003; Iversen 2006; Nutt 2006; Parrott 2001; Saunders 1997).

There are, however, several crucial issues which need to be addressed before it can be concluded that MDMA has an appropriate pharmacological profile for a therapeutic drug (Tables 1, 2, 3). Firstly, acute MDMA can intensify both positive and negative material, and some individuals find the negative experiences distressing. Secondly, the emergent material is susceptible to environmental factors; indeed, psychotherapists have suggested that set and expectancy may be more crucial than the drug itself (Metzner and Adamson 2001). This again limits its practical utility, as it may be difficult to ensure the appropriate preparation of client and therapist. So that abreactions can occur, even in the presence of an experienced psychotherapist, and after following the recommended preparatory procedures (Greer and Tolbert 1986, 1990). Thirdly, there is the period of neurochemical recovery after MDMA usage, when negative moods and cognitions predominate, and these may be therapeutically counter-productive. Fourthly, it may be inadvisable to administer CNS stimulants such as MDMA to psychiatrically vulnerable individuals (Table 2). The prime concern is that a psychiatric predisposition may increase the likelihood of acute and chronic drug abreactions. This is well established with other CNS stimulants (Dittrich 1994), and psychotherapists have noted that it can also occur with MDMA (Greer and Tolbert 1986).

The main problem, however, is that there is no clear neurochemical model for how MDMA can relieve psychiatric distress. The explanations which have been proposed are all psychodynamic, as most of the advocates for MDMA-assisted therapy are psychotherapists (Doblin 2002; Greer and Tolbert 1986; Grinspoon and Bakalar 1986; Mithoefer 2005). They suggest that MDMA is entactogenic, that it stimulates the release of negative-troublesome material from the past, and it fosters the bonding between client and therapist (Table 1). The psychodynamic models also suggest that a single session of MDMA-assisted therapy can lead to enduring changes. Neurochemical explanations for all the above proposals need to be described more comprehensively. This would allow the potential benefits and drawbacks of using CNS stimulant drugs in psychotherapy to be stated more clearly (Table 3). To summarize, MDMA has a great deal of superficial charm, but a detailed analysis of its pharmacodynamic profile shows that there are many core problems which would need to be answered before it can be concluded that MDMA might be clinically useful for psychiatric patients seeking therapy.

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