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### Book chapter :

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## Abstract

In chapter fifteen, 'Clinical and medical management of conditions caused by MDMA or "Ecstasy"', Andrew Parrott provides an overview of the evolution of the MDMA market over the years, which has become increasingly more complex and multifaceted with the introduction of products containing very high doses of MDMA or substances passed as MDMA but actually containing a series of different products. A detailed analysis of incidences, dangers, and available treatments has been provided as well as a review of causes of death and prevention strategies. Andrew Parrott will also discuss the clinical presentation of toxicity and clinical management strategies for clinicians.

## Running Head Right-hand: Management of Conditions Caused by MDMA

Running Head Left-hand: Andrew C. Parrott

15

### Clinical and Medical Management of Conditions Caused by MDMA or 'Ecstasy'

Andrew C. Parrott

#### **Introduction**

The United Nations Office on Drugs and Crime (2018) noted that the term 'novel psychoactive substances' (NPS) had first been used around ten years previously. It reflected the dramatic expansion in novel substances becoming available to illicit drug users. On average, one new drug was uncovered by the professional drug agencies every week (UNODC, 2018). The use of the Internet and the dark web allowed drug users to purchase these novel substances very easily and have them delivered to their homes by the normal postal delivery services (Corazza, Schifano, & Parrott, 2013). The illicit drug scene was changing rapidly, and this was generating many new problems for the professional drug agencies. Several international conferences on this NPS phenomenon have been organized in recent years. The first was in Budapest (2011), followed by Swansea (2013), Rome (2014), and then again in Budapest (2016). The fifth conference was held at the United Nations in Vienna (2017), confirming the international importance of this problem. The papers from these meetings have been published in a series of special issues of the journal *Human Psychopharmacology* (Corazza et al., 2013; Corazza, Parrott, & Demetrovics, 2017; Parrott & Corazza, 2013).

The UNODC (2018) report noted that 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy) was perhaps the first of these novel substances, although it was now well established. The report noted that in recent years the Ecstasy/MDMA market had become increasingly complex and multifaceted; some of the illicit supplies demonstrated an 'extremely high MDMA content', while some

illegal drug factories in Europe were producing supplies on an industrial scale [note: the increasing death rates from recreational MDMA in recent years are debated more fully later]. When MDMA was first used as a recreational drug in the 1980s and 1990s, it was often misperceived as a relatively safe drug, since most of its damaging psychobiological effects were not then known. However, in the past thirty years, numerous scientific studies have revealed that MDMA has a wide range of damaging effects on human wellbeing (Parrott, 2001, 2006, 2013a, 2013b, 2015). The aim of this article is to summarize these acute and chronic dangers and recommend methods for their management and treatment.

### **Broad Overview of the Adverse Effects of MDMA**

This section will briefly overview the main dangers from recreational MDMA. It should be noted that these problems will be described more fully in later sections, where full reference support will be provided. Hyperthermia is experienced by most dance clubbers on MDMA, with average body temperature increases of around +1.0°C. More severe overheating (body temperature +40°C) requires rapid cooling by air fans or ice baths, since without urgent medical intervention, this hyperthermia can be fatal. MDMA also impairs fluid control, with excessive fluid intake and retention causing hyponatraemia, the dilution of sodium electrolytes. Mild hyponatraemia had been found in 25% of female and 3% of male dance clubbers. Treatment involves the rapid re-establishment of normal sodium levels intravenously, since severe hyponatraemia can be fatal. Other acute abreactions to MDMA include cardiac distress, heart attack, brain haemorrhage, and liver damage, with severe cases requiring liver transplantation. Disseminated intravascular coagulation may result in uncontrollable bleeding from multiple orifices, when death may be rapid. Most acute medical emergencies are treated successfully, although around 60 MDMA deaths occur in Great Britain each year, and international death rates are increasing.

The chronic or repeated use of MDMA causes a range of neuropsychobiological problems. The repetitive overstimulation of the body and brain causes cumulative bio-energetic stress, which impairs

key biological functions and disrupts homeostasis. The serotonergic neurotransmitter system in the brain is chronically damaged, a phenomenon termed 'serotonergic neurotoxicity'. The stress hormone cortisol is increased by an average of 400% in three-month hair samples of regular Ecstasy/MDMA users. Biochemical markers of oxidative stress are increased, and white blood cell counts reduced. Thermal control may be reduced in chronic users, with practical implications for the lives of military personnel. Physical activity in hot conditions may exacerbate hyperthermia, while cold immersion may lead to excessive overcooling or hypothermia. Sleep problems are noted by 70% of recreational Ecstasy/MDMA users, with sleep apnoea developing in a minority. MDMA can lead to heightened depression, and other psychiatric problems, including stress, anxiety, impulsivity, anger, and physical aggression. For clinical management, the optimal treatment is drug cessation. Empirical research has shown that quitting Ecstasy/MDMA can lead to improved mental health. In neurocognitive terms, the recreational use of MDMA leads to disorders of memory and reduced cognitive skills. Even simple occupational tasks like 'office work' can be impaired. These neurocognitive impairments endure for several years post-cessation and may well be permanent. Basic cognitive skills are however retained. Psychomotor problems and reduced steadiness can develop in adults. Psychomotor retardation occurs in babies born to mothers who took recreational MDMA during pregnancy.

All recreational CNS stimulants can lead to dependency, although this is less characteristic of MDMA. This is because the cost-benefit ratio deteriorates naturally, with repeated MDMA usage leading to weaker mood gains and stronger adverse effects. Hence most users quit on their own, although heavy users and bingers may need professional assistance. Cognitive guidance and insight therapy can explain how the drug is damaging and why abstinence is important. Clinical management should focus on developing new life skills which do not involve drug taking, since former users have an increased risk of developing other drug dependencies. Prevention is by far the safest option, with young people needing clear information about its damaging effects. The best practical advice is to never take MDMA.

Table 15.1 Overview of Acute Medical Abreactions to MDMA and Their Treatment

[Note to author: Tables are better viewed when changing your 'MS Word settings' to 'Web view'].

Acute Abreaction	Incidence-Occurrence	Management-Treatment	References
Moderate thermal stress and increased body temperature	Most recreational users at dances or parties	If feeling hot, stop dancing. Avoid overheating since it can contribute to cumulative drug damage.	Freedman et al., 2005.  Parrott, 2002, 2006.  Morefield et al., 2009.  Parrott & Young, 2015.
Severe overheating and hyperthermia	Case studies and reports, potentially lethal if not treated rapidly	Take to hospital immediately; rapid cooling, ice baths, intravenous dantrolene.	Hall & Henry, 2006.  Patel, Belson, Longwater, Olson, & Miller, 2005  Greene, Wood, & Dargan, 2009
Mild hyponatraemia (sodium electrolyte dilution in blood)	25% of females and 3% of males at dance clubs	Do not drink any more fluids. Seek medical blood testing. Do not take MDMA again.	Van Dijken et al., 2013.  Baggott et al., 2016

Strong hyponatraemia  (more severe sodium depletion in blood)	Case reports and medical surveys, potentially lethal if not treated rapidly	Seek urgent blood test, intravenous sodium immediately.	Hall & Henry, 2006. Rosenson et al., 2007.  Halpern et al., 2011
Serotonin syndrome	Mild syndrome usual for recreational users, strong syndrome in a minority	Rest and recover. Do not take other serotonergic drugs. Do not take MDMA again.	Parrott, 2002, 2006.
Chronic tolerance	Dosage escalation very common, bingeing in experienced users, heavy users may inject	Generally self-limiting. Most users quit on their own as the cost-benefit ratio deteriorates.	Topp, Hando, Dillon, Roche, & Solowij, 1999  Fox, Parrott, & Turner, 2001  Parrott, 2005, 2010.  Downey et al., 2017
Cardiac problems, liver failure, single and multi-organ failure	Severe abreactions rare or unusual, mild abreactions may be underreported	Seek standard medical treatments, liver transplantation, blood platelets to reverse uncontrollable bleeding.	Smith, Simpson, Garden, & Wigmore, 2005.  Hall & Henry, 2006

Cortisol increase	Group increase of 800% in dance clubbers	Stop dancing, and rest.	Parrott, Lock, Conner, Kissling, & Thome, 2008  Parrott, 2009, 2016
Death	Around 60/year in UK, international death rates may be increasing	Do not take MDMA again.	Chadwick, Curry, Linsley, Freemont, & Doran, 1991.  Schifano et al., 2010.  Santacroce et al., 2017

**Neurotransmitter and Neurohormonal Effects of MDMA**

The chemical name for MDMA is 3,4-methylenedioxymethamphetamine, which identifies it as a methamphetamine derivative. Indeed, MDMA displays many psychophysiological similarities to other recreational stimulant drugs, such as methamphetamine, amphetamine, and cocaine (McDowell & Kleber, 1994; Ricaurte, Yuan, & McCann, 2000; Parrott, 2008, 2015). Its effects on dopamine and noradrenaline lead to stimulatory effects, such as greater alertness and more intense moods. Hence in laboratory studies, acute MDMA leads to increased heart rate, faster breathing, and heightened blood pressure (Liechti, Gamma, & Vollenweider, 2001). At dance clubs and raves, the stimulatory effects can be much stronger because of the interactive effects of taking a stimulant drug in hot and overcrowded conditions—while dancing vigorously (Parrott, 2002, 2004). Many recreational users feel highly aroused, with one person stating that he or she felt as if there were a ‘stereo inside my body’ (Cohen, 1998; Parrott, 2010).



Unlike the more traditional CNS amphetamines, MDMA displays a strong affinity for the serotonin transporter (SERT). Hence an acute dose of MDMA reverses normal serotonin reuptake and generates a large efflux of serotonin into the synaptic cleft (Berger, Gu, & Azmitia, 1992). This heightened stimulation is accompanied by elements of the serotonin syndrome, with 'hyperactivity, mental confusion, hyperthermia, and trismus (jaw clenching), being typical on-drug experiences for most Ecstasy users' (Parrott, 2002). MDMA can be especially dangerous if combined with other serotonergic drugs or medicines. Chronic or repeated MDMA can adversely affect the integrity of the serotonergic system. In laboratory animals, this leads to a pattern of selective changes to the distal serotonin axon terminals (Puerta, Hervias, & Aguirre, 2009); this is often termed 'serotonergic neurotoxicity', although there is debate over the exact nature of these serotonergic changes. Biezonski and Meyer (2011) noted that some explanatory models suggest distal axon terminal loss, while other models suggest neuroadaptive changes. Despite the different models, it was noted that the empirical evidence for MDMA-induced serotonergic depletion was overwhelming. Hence Biezonski and Meyer (2011) concluded that MDMA was certainly 'neurotoxic'—in that it impaired the serotonergic system. Similar conclusions have been offered by Reneman, de Win, van den Brink, Booij, and den Heeten (2006), Puerta et al. (2009), Benningfield and Cowan (2013). The following articles should also be consulted (McCann et al., 2008; Kish et al., 2010; Erritzoe et al., 2011; Di Iorio et al., 2012; Yegting et al., 2016), where they also debate the complex issue of whether this damage is permanent.

The hypothalamic-pituitary-adrenal (HPA) axis is crucial for homeostasis, the everyday maintenance of psychological balance, and physiological health. The master neurohormone for homeostatic control is cortisol, and this is strongly affected by acute and chronic MDMA. In placebo-controlled laboratory trials, an acute dose of MDMA generates a cortisol increase of around 100–200% 1–3 hours later (Harris, Baggott, Mendelson, Mendelson, & Jones, 2002; Dumont & Verkes, 2006). When taken at dance clubs, the increase in cortisol can peak at around 800% of baseline values (Parrott, 2016). This dramatic cortisol increase was originally found in dance clubbers who had self-administered Ecstasy,

with MDMA being biochemically confirmed (Parrott et al., 2008). No changes in cortisol were found when the same participants went dance clubbing off-MDMA (Figure 15.1). In a parallel house-party study, an almost identical peak cortisol increase of 800% again emerged (Parrott et al., 2007). These pronounced increases in cortisol were far greater than those found in most situations. For instance, the standard psychophysiological stress test of 'cycling to exhaustion', leads to a peak cortisol increase of around 80–140% (for relevant studies, see reviews by Parrott (2009, 2016). MDMA can also induce changes in other neurohormones, including oxytocin, testosterone, and prolactin (Figure 15.1; review—Parrott, 2016).

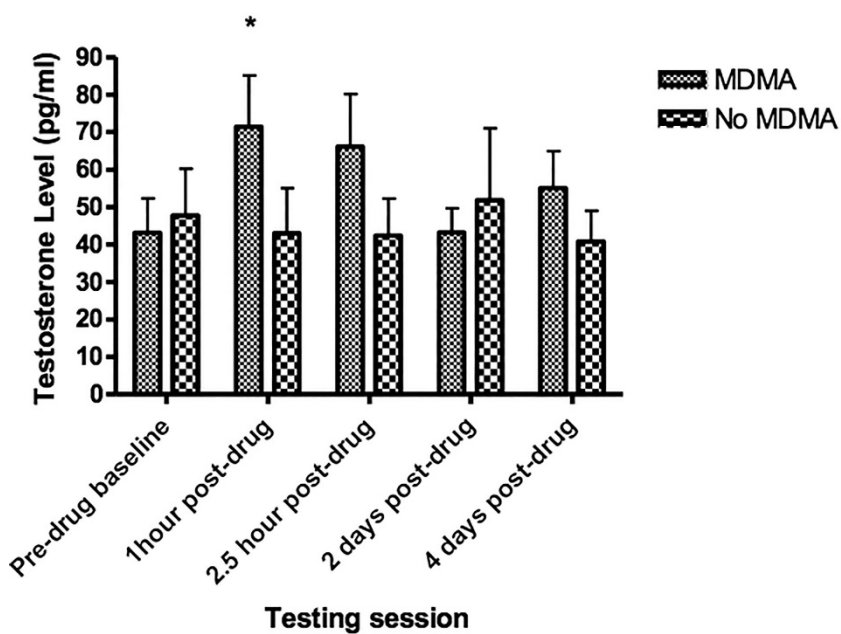
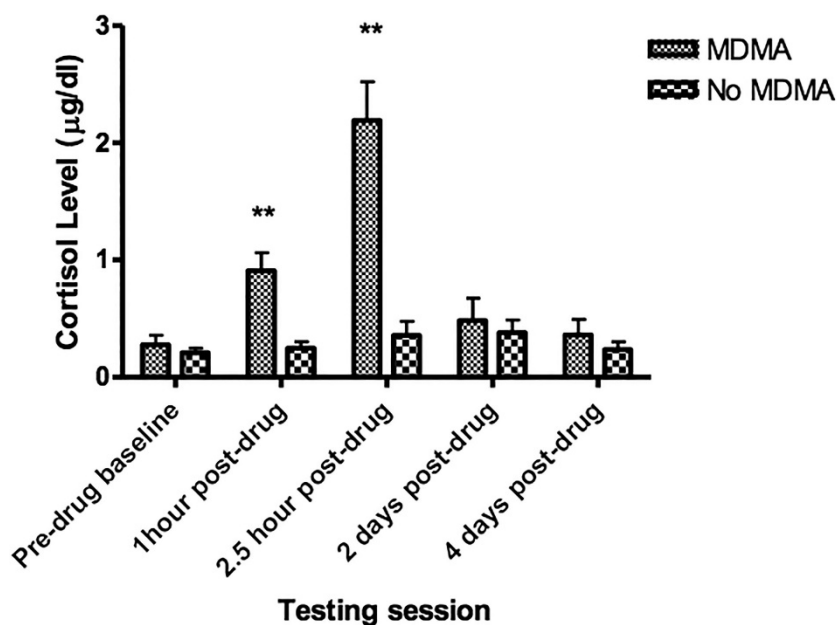


Figure 15.1 Cortisol and Testosterone Levels of Recreational Ecstasy/MDMA Users Dance-Clubbing. Twelve unpaid volunteers were

assessed on self-administered MDMA, and while abstaining from MDMA, over counterbalanced weekends at the same dance club venue, with the same group of friends. P-levels represent paired comparisons with the pre-drug baseline (after: Parrott et al., 2008)

The repeated use of MDMA can also lead to enduring changes in cortisol reactivity (Gerra et al., 2003; Verkes et al., 2001). Baseline cortisol levels may be changed, and cortisol responses to stress altered (Gerra et al., 2003). Wetherell and Montgomery (2014) found that the cortisol awakening response was significantly higher in drug-free Ecstasy/MDMA users on a high-stress day, with cortisol levels late at night also raised. Frokjaer et al. (2014) similarly found an increase in the cortisol awakening response with regular Ecstasy/MDMA users, while this enhanced cortisol response was associated with greater prefrontal binding of the serotonin transporter (see previous section on neurotoxicity). Parrott et al. (2014a) found 400% higher levels of cortisol in the hair of recent regular Ecstasy/MDMA users, while light/minimal recent users also showed a trend for higher cortisol levels. Hence there are various indications of altered stress reactivity, with MDMA-induced changes to both the neurotransmitter and neurohormonal systems. Acute and chronic MDMA can lead to a range of functional abreaactions, with damage to many different aspects of physical and psychological health. The following sections will focus on these abreaactions and their clinical management.

### **Hyperthermia: Incidence, Dangers, and Medical Treatment**

MDMA can cause thermal stress and overheating. In the laboratory, Freedman et al. (2005) reported that acute MDMA generated a significant increase in core body temperature, with 2.0 mg/kg leading a mean peak increase of 0.7°C. In laboratory studies, these thermal increases are dose related, with higher doses leading to higher core body temperatures (see summary table 2 in Parrott, 2012). Most recreational Ecstasy/MDMA users report feeling hot, sweaty, or dehydrated (Davison & Parrott, 1997; Topp et al., 1999; Parrott et al., 2008). One American dance clubber on MDMA noted that ‘it feels like your blood is 115 degrees Fahrenheit’ (Cohen, 1998). With Australian party goers, Morefield, Keane, Felgate, White, and Irvine (2009) found a

group mean body temperature increase of +1.1°C and an average skin temperature increase of +1.8°C. In a similar UK study, the group mean peak increase was +1.2°C (Parrott & Young, 2015), although other studies found smaller increases (review: Parrott, 2012). Many dance clubbers visit the 'chill-out' room to rest and recover, although some continue to dance for prolonged periods (Suy, Gijzenbergh, & Baute, 1999), or dance continuously with minimal breaks (Parrott et al., 2006).

In some recreational MDMA users, the hyperthermia can be severe and may require medical intervention to prevent a fatal outcome. The first documented case study of successful medical intervention was outlined by Brown and Osterloh (1987). A young woman was admitted to hospital two hours after taking 100–150mg of MDMA powders. Her body temperature on admission was 41.6°C, and this hyperthermia was soon reduced by ice packs. In the following days, rhabdomyolysis, coagulopathy, visual hallucinations, toxic hepatitis, and a herpes-like skin rash developed. Intensive care was successful and led eventually to her medical discharge. Chromatography revealed pure MDMA in the powders she had taken, and toxicological analysis revealed that no other drugs had been consumed. The friend who took her to hospital had taken the same MDMA powders, without a pronounced thermal reaction, while both women had taken MDMA previously. The first documented MDMA-hyperthermic fatality was described by Chadwick et al. (1991). A 16-year-old girl was admitted to hospital with an axillary temperature of 40°C and a provisional diagnosis of amphetamine overdose. Two hours later, the axillary temperature had increased to 42°C, and with fresh oral bleeding, she was moved to the intensive care unit. Intubation and ventilation were accompanied by haemodynamic monitoring and multiple medical interventions, including 35 units of blood and 21 units of platelets. The patient died 36 hours after admission. Toxicological analysis revealed 0.424 mg/l MDMA on admission, with no other drugs. Police enquires revealed that she had taken a single tablet of Ecstasy—and that this was her second Ecstasy/MDMA experience.

Further MDMA fatalities due to hyperthermia were described by Henry, Jeffries and Dawling (1992). The body temperatures on hospital

admission ranged between 40–43°C, and they displayed similar patterns of hyperthermic abreaction, including disseminated intravascular coagulation, rhabdomyolysis, and acute renal failure. The dosage levels varied considerably; the lowest plasma MDMA level was 0.11mg/l, while the highest was 1.26mg/l. In just one case, other psychoactive drugs were present, with low levels of amphetamine and MDA. Henry et al. (1992) also described four cases where initial body temperatures were around 40°C, with intensive medical intervention being successful. Patel et al. (2005) described six case studies of MDMA-related hyperthermia, including three individuals who had been at the same rave party. The first was a 20-year-old woman who was found unresponsive at the party. Her skin felt ‘very hot’ to the touch, and intensive resuscitation was immediately attempted but was unsuccessful. Toxicological analysis revealed 1.21 mg/l MDMA and 0.40 mg/L methamphetamine. The second case was a 20-year-old male in a coma, with hot, dry skin and an oral temperature of 41.5°C. Intensive medical intervention with rapid physical cooling in an ice bath reduced his temperature to 38.1°C, and he was discharged. Urine toxicology revealed MDMA alone; subsequent discussions revealed that he had previously taken similar amounts of Ecstasy/MDMA without adverse reactions. A third emergency hospital admission needed physical restraint by the police. Cooling blankets, ice baths, and isotonic intravenous liquids reduced the high temperature of 40.7°C on admission. Laboratory analysis revealed that the Ecstasy pills contained pure MDMA. Many other cases of MDMA-induced hyperthermia have been described, often with successful medical intervention, although some resulted in fatalities (Corre, 1996;; Schifano et al., 2003, 2010; Grunau, Wiens, & Brubacher, 2010).

The core treatment for MDMA-hyperthermia is rapid cooling (; Rusyniak and Sprague, 2005; Grunau et al., 2010). In a medical article, Hall and Henry (2006) described the different type of thermal abreaction caused by MDMA and outlined the treatment options for the accompanying hyperpyrexia and multi-organ failure. They noted that ‘Patients with acute MDMA toxicity may present to doctors working in Anaesthesia, Intensive Care and Emergency Medicine. A broad knowledge of these pathologies and their treatment is necessary for those working in an acute medicine speciality’. In an Israeli study, Halpern et al. (2011)

summarized the medical profiles of MDMA-related emergency hospital admissions. Common manifestations included restlessness, agitation, disorientation, shaking, high blood pressure, headache, and loss of consciousness; while more serious cases involved severe hyperthermia (and hyponatraemia—see next section). The authors emphasized that in their experience, the widespread perception of Ecstasy as a safe party drug was ‘spurious’. Grunau et al. (2010) recommended the use of dantrolene in cases of severe (<40.0°C) or extreme (<42.0°C) hyperthermia. For more moderate hyperthermia, the standard approach was immediate cooling with air fans or ice baths. Greene et al. (2009) reviewed 332 MDMA-related admissions to the emergency department of one London Hospital over a three-year period. Core body temperatures on admission ranged from very low (34.1°C) to very high (41.6°C). The cases of low temperature reflect the core fact that MDMA impairs thermoregulation, so that in cold environments, the body cools excessively. Medical treatment in such cases is immediate warming (e.g., into a warm bed vacated by another patient!)

Table 15.2 Overview of Chronic Problems Caused by Repeated Ecstasy/MDMA and Their Treatment

Chronic Problem	Occurrence	Management-Treatment	References
Memory deficits	In most regular users; stronger deficits in heavier users; enduring problems over time	Stop taking MDMA. Develop practical skills such as note taking.	Krystal, Price,, Opsahl, Ricaurte, & Heninger, 1992  Spatt, Glawar, & Mamoli, 1997.  Parrott, Lees, Garnham,

			<p>Jones, &amp; Wesnes, 1998.</p> <p>Laws &amp; Kokkalis, 2007</p> <p>Wunderli et al., 2017.</p>
Prospective memory deficits	Commonly reported, dosage-related, more problems in heavier users	<p>Stop taking MDMA.</p> <p>Develop practical skills.</p> <p>Use diaries and/or electronic planners.</p>	<p>Heffernan, Jarvis, Rodgers, Scholey, &amp; Ling, 2001</p> <p>Rendell, Gray, Henry, &amp; Tolan, 2007</p> <p>Montgomery, Hatton, Fisk, Ogden, &amp; Jansari, 2010</p> <p>Parrott, 2013a,b</p>
Simple cognitive skills	Not impaired	No treatment required.	<p>Mc Cann et al., 199-98.</p> <p>Parrott et al., 1998</p>
Higher cognitive deficits and	Found in moderate and heavier users.	Some heavy users may need to move to simpler	Fox et al., 2001, 2002.



reduced problem-solving abilities		occupations/employments. Stop taking MDMA.	Fisk, Montgomery, Wareing, & Murphy, 2005.  Taurah, Chandler, & Sanders, 2013  Parrott, 2013b
Brain changes (ERPs, fMRI, other indices)	Mostly in moderate or heavy users; light users less impaired	Many users compensate by putting more effort into task performance. Stop taking MDMA.	Reneman et al., 2006.  Kish et al., 2010  Burgess et al., 2011.  Roberts, Quednow, Montgomery, & Parrott, 2017
Psychiatric problems: depression, anxiety, anger, aggression	Mild to moderate distress in many regular users; more severe problems in some individuals	Cessation of MDMA can reverse the psychiatric deficits.	Schifano et al., 1998.  Parrott et al., 2000, 2001  Verheyden et al., 2003

			Briere et al., 2012.  Turner et al., 2014
Sleep impairment	Around 70% of recreational users	Stop taking MDMA. Read more books at night?	McCann & Ricaurte, 2007  Ogeil, Rajaratnam , & Broadbear, 2013
Sleep apnoea	Minority of regular users	Stop taking MDMA. No known therapy.	McCann, Sgambati, Schwartz, & Ricaurte, 2009.
Cortisol and HPA axis	400% increase in hair cortisol samples, impaired homeostasis	Many adverse implications of altered HPA axis. Stop taking MDMA.	Gerra et al., 2003.  Parrott, 2009, 2016  Parrott et al., 2014a,b
Dental problems	Excessive chewing, worn down molars, hole in chewed skin below mouth.	Stop taking MDMA.  Dental restoration is limited; facial restoration is limited.	Redfearn, Agrawal, & Mair, 1998  Nugent, Basyuni, McAnerney , &

			Cameron, 2017
Foetal abnormalities	Cardiovascular and musculoskeletal anomalies	Do not take MDMA without contraception.	McElhatton et al., 1999
Neonates: delayed psychomotor development	Prospective study of women who took MDMA during pregnancy	Females should not take MDMA during conception or pregnancy. Males should not take MDMA during conception.	Singer, Moore, & Fulton, 2012; Singer, Moore, & Min, 2012; Singer et al., 2015

Another important question is whether chronic MDMA damages thermoregulatory ability. There is a paucity of empirical data on this question, although some indirect evidence. Parrott and Young (2015) measured body temperatures of dance clubbers and found raised temperatures in current MDMA users compared to never-user controls who were mostly alcohol drinkers. The third group comprised dancers who had not taken MDMA that weekend but who had taken it previously. Their body temperatures were significantly raised in comparison to the never-user controls, suggesting that the previous use of MDMA had impaired their thermoregulatory abilities. In a recent British legal case, a soldier who had taken MDMA 3 days previously died of heatstroke when subjected to physical exercise on a hot day. The court case focused on the residual effects of acute MDMA. As an expert witness, I agreed that this was certainly important. However, I also noted that any impairment in thermoregulatory ability might also reflect the effects of chronic MDMA. Empirical research is required to test this hypothesis. Certainly, the armed forces may need a better understanding of this issue, given that hyperthermia (prolonged military exertions in hot countries) and hypothermia (fighting in arctic

conditions, downed aircrew in cold sea emersions) are potentially lethal occupational hazards of military personnel.

### **Hyponatraemia: Incidence Rates, Health Dangers, and Treatment**

When feeling hot and thirsty, many recreational MDMA users drink large amounts of water. This can lead to hyponatraemia, or the dilution of sodium electrolytes in the blood serum (Halpern et al., 2011; Baggott et al., 2016). The effects of excessive fluid intake may be compounded by changes in the anti-diuretic hormone, which reduces micturation (peeing) and further contributes to this electrolyte dilution. Hence hyponatraemia is a hazard for all recreational Ecstasy/MDMA users. At one Dutch rave, Van Dijken, Blom, Hene, and Boer (2013) took blood samples from volunteers in order to measure their plasma sodium levels. This revealed mild hyponatraemia ( $\text{Na} < 130 \text{ mmol/L}$ ) in 25% of the female MDMA subgroup, compared to 3% of the male subgroup. This gender difference was apparent despite similar rates of Ecstasy/MDMA consumption. Gender differences had also been noted in an earlier American study, where 17 of the 18 documented hyponatraemia cases were female (Budisavljevic, Stewart, Sahn, & Ploth, 2003). The California Poisons Unit reviewed 1,407 cases of MDMA-attributed hyponatraemia which were reported from 2000–2005 (Rosenson et al., 2007). Full data was lacking in most cases, but where blood samples had been taken, clinically confirmed hyponatraemia was significantly more evident in females. Other amphetamine drugs were present in some cases, while females also displayed an increased risk of hyponatraemia-with-coma. Potential reasons for the gender imbalance were lower female body weight (viz: resulting in higher drug concentrations) and neurohormonal factors. Cortisol, oxytocin, and many other neurohormones are known to be affected by MDMA (Parrott, 2006; see earlier section), and gender may be a co-factor. The menstrual cycle affects psychobiological reactions to nicotine (Craig et al., 1993) and may influence responses to many other drugs including MDMA.

For optimal clinical management, blood electrolyte levels should be assessed on admission and sodium levels restored immediately (Hall & Henry, 2006; Halpern et al., 2011). Rapid intervention can be very

successful, although hyponatraemia may prove lethal if not reversed in time. Many cases are brought to the attention of the emergency medical services too late, with resulting fatalities. Schifano et al. (2010) analyzed the government data on recreational stimulant deaths in the UK between 1997 and 2007. Over this period, there were 832 deaths related to amphetamine or methamphetamine and 605 related to Ecstasy/MDMA. Many were related to multiple drug ingestion or 'polydrug' use. However, in the analysis of 'mono-intoxication' fatalities, Schifano et al. (2010) found that deaths following Ecstasy/MDMA alone were significantly overrepresented in comparison with deaths following amphetamine or methamphetamine alone (when considered in relation to overall usage rates). There are also indications of increasing death rates recently. For instance, on the 'party island' of Ibiza, acute deaths due to Ecstasy/MDMA and cocaine increased significantly from 2010 to 2015 (Santacroce et al., 2017).

### **Causes of Death: Medical Treatments and Prevention Strategies**

Hall and Henry (2006) reviewed the medical scenarios and treatment options for physicians working in emergency medicine. They noted that

Hyperpyrexia and multi-organ failure are now relatively well-known, other serious effects have become apparent more recently. Patients with acute MDMA toxicity may present to doctors working in Anaesthesia, Intensive Care and Emergency Medicine. A broad knowledge of these pathologies and their treatment is necessary for those working in an acute medicine speciality.

They noted that MDMA can cause death by various forms of organ failure. In laboratory studies with animal liver tissue, MDMA can induce apoptosis or programmed cell death (see reviews Parrott, 2013a, 2013b), with some recreational users suffering from fatal liver failure. Smith et al. (2005) described case studies of young people whose livers had been damaged by acute MDMA, with some then requiring emergency liver transplantation. Other fatalities result from cardiac arrest, brain seizure, and rhabdomyolysis or the destruction of skeletal muscle tissue. Some of the previous case studies in this chapter have summarized the emergency medical interventions, both successful and

unsuccessful. One frequently lethal outcome is disseminated intravascular coagulation or DIC, where the failure of blood clotting leads to uncontrollable bleeding through multiple sites (Henry et al., 1992; Hall & Henry, 2006).

### **Tolerance, Dependency, and Therapeutic Potential**

Shulgin (1986) suggested that 'MDMA does not lend itself to overuse because its most desirable effects diminish with frequency of use'. Many other early reports suggested that MDMA was unique in this aspect, further noting that tolerance reduced its abuse liability. In an interview study with early American MDMA users, Peroutka, Newman, and Harris (1988) noted that its positive effects were said to decline with repeated usage, as its adverse effects increased. In a UK study from 1992–3, recreational users reported that they took MDMA-free breaks of several weeks in order to minimize 'drug habituation' (Davison & Parrott, 1997). However, many regular users just increase their dosing. Fox et al. (2001) found that the maximum single session dosage increased from 3.6 tablets in light users to 5.5 tablets in moderate users and 10.9 in heavy users. For more studies on dosage escalation, see the review by Parrott (2005). Hammersley, Ditton, Smith, and Short (1999) reported that MDMA bingeing was noted by 76% of heavier users, compared to 16% of light users. This more intensive Ecstasy/MDMA usage led to more days-off work because of illness, reduced appetite, and more episodes of depression. Some patterns of bingeing were quite extreme, with repeated MDMA self-dosing for 48 hours or more without sleep (Topp et al., 1999). Some very experienced users inject MDMA (Topp et al., 1999; Downey et al. (2017)), although the hit can be 'too intense to enjoy' and the post-drug comedown even worse than usual.

Every CNS stimulant drug has addiction potential, although MDMA has a comparatively low potential—for two reasons. The most addictive stimulant drugs have a rapid hit—followed by a rapid comedown; hence the highest addiction potentials are displayed by crack cocaine and ice methamphetamine (Parrott, 2015). In contrast, the initial effects of oral MDMA develop slowly and are followed by a long-lasting comedown period of several days (Parrott & Lasky, 1998). Hence MDMA tends to be

used infrequently, most typically less than once a week (Parrott, 2005). Secondly, MDMA damages the serotonin system (Kish et al., 2010; Benningfield & Cowan, 2013), and this reduces its efficacy over time. Hence regular users take the drug less frequently than novice users, before ceasing usage (review: Parrott, 2005). Because of this low addiction potential, drug addiction centres are rarely attended by individuals seeking help for MDMA dependency. This leads some addiction experts to believe that MDMA is not a problematic drug. This belief is mistaken, since while MDMA displays low addiction potential, it does cause a wide range of other neuropsychobiological problems, as listed in Table 15.2 (Topp et al., 1999; Parrott, 2000, 2001, 2006, 2013a.b).

MDMA has been assessed as a drug-adjunct for psychotherapy, and most reports in this field have focused on its potential benefits (Mithoefer, Bateman, Evans, Pughe, & Thomas, 2016; Wagner et al., 2017). However, there are many potential dangers from using this powerful CNS stimulant drug, and even in the restful therapeutic environment, clinical casualties have been reported (Greer & Tolbert, 1986; Parrott, 2007, 2014, 2018). The first detailed report of MDMA-assisted therapy was by Greer and Tolbert (1986), and they noted that all 29 clients reported some positive gains, but every client also reported some negative experiences. In relation to overall balance, while some clients reported overall benefits from MDMA, others had more negative overall experiences. In particular, some individuals with pre-existing psychiatric problems experienced a reoccurrence of symptoms. This led Greer and Tolbert (1986) to conclude 'There is an indication that MDMA may predispose people to a recurrence of previous psychological disabilities'. Another potential problem is dosage escalation. One of their clients did not respond positively to the normal dose, so he or she was given a higher dose of MDMA. This generated a severe abreaction, with side effects which included 'nausea, small amount of vomiting, jaw tension, ataxia, urinary urgency, blurred vision, sweating, brief short-term memory loss, brief distortion of depth perception with a brief hallucination'. Despite this severe abreaction, dosage escalation in non-responsive clients has also occurred more recently (see Parrott, 2018). Further information on the potential

problems of MDMA-assisted psychotherapy are contained in the following reviews (Parrott, 2007, 2014, 2018).

### **Psychiatric Disturbances**

MDMA has acute and chronic effects on the serotonin system and the HPA axis. Hence it is not surprising that it can exacerbate various psychiatric conditions (Cowan & Lucki, 2011; Parrott, 2013a, 2013b; Parrott & Lasky, 1998; Parrott et al., 2000, 2001, 2014a,b). Schifano et al. (1998) found that regular MDMA users reported various psychopathological problems, including depression, psychotic disorders, feelings of panic, problems with impulse control, and eating disorders. MacInnes, Handley, and Harding (2001) found significantly higher depression scores in Ecstasy/MDMA users than non-user controls, despite all participants being screened for previous psychiatric distress. In a statistical review, Rogers et al. (2009) found that problems with depression, impulsivity, and anxiety were significantly worse for Ecstasy/MDMA users than for polydrug controls. Briere et al. (2012) prospectively monitored 3,880 disadvantaged schoolchildren in Canada; those children who started taking MDMA reported significantly higher depression one year later. Scholey et al. (2010) found that abstinent Ecstasy/MDMA users reported feeling significantly more stressed than non-user controls. Wetherell et al. (2012) reported that abstinent users were significantly less calm when performing a stress-induction task. Reid, Elifson, and Sterk (2007) found increased hostility and aggression in heavier Ecstasy/MDMA lifetime users and questioned whether MDMA was best described as a 'hug drug' or as a 'thug drug'. Gerra et al. (2001) found that the heavier lifetime Ecstasy/MDMA users showed more aggressive reactions to a standard behavioural aggression task. In a large American population survey, Vaughn, Salas-Wright, DeLisi, Perron, and Cordova (2015) found that MDMA users were involved in more crimes of violence and crimes of non-violence than non-users. This was found in both genders, with female MDMA users being more antisocial than male non-users. Rugani et al. (2012) studied clinical cases of acute psychosis at an Italian psychiatric hospital. Those who had taken Ecstasy/MDMA reported significantly higher levels of hostility, physical violence, and verbal aggression. This led to the following



conclusion: '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'.

In relation to therapy, I am not aware of any study that has specifically investigated MDMA users. Hence psychiatrists are advised to follow the normal therapeutic procedures, for each form of psychiatric condition. One crucial piece of advice is to stop taking MDMA, since it is well established that the incidence of problems increases with greater lifetime usage (Kish et al., 2010; Parrott, 2013a, 2013b). Yet in order for this practice to become usual, psychiatrists and physicians need to be educated about its adverse effects. Mental health improves after cessation of other recreational stimulants, such as amphetamines or cocaine, and similar gains have been found following Ecstasy/MDMA cessation (Parrott, 2015; Parrott, Hayley et al., 2017). Morgan, McFie, Fleetwood, and Robinson (2002) found that current and former MDMA users displayed heightened psychopathology scores, while former users were less impaired. Verheyden, Maidment, and Curran (2003) also found that 70% of former Ecstasy users reported 'improved mental health' after quitting the drug. In a two-year prospective study, Turner et al. (2014) found that young mothers who quit using MDMA reported significantly reduced depression rates 18 months later. Indeed their heightened Brief Symptom Inventory depression scores as MDMA users returned to control group values following cessation. However, not all studies report psychiatric gains, with Taurah et al. (2013) finding that depression scores remained significantly raised in former MDMA users.

### Neurocognitive Deficits

The first chronic deficits to be empirically described in recreational Ecstasy/MDMA users were problems with memory (McCann and Ricaurte, 1991; Krystal et al., 1992). Performance deficits on standard cognitive tests of memory were subsequently confirmed in the first cohort studies, with impairments in immediate and delayed word recall (Parrott et al., 1998) and impaired prose recall (Morgan, 1999). An early review of 20 published studies found deficits with many different memory tasks (Parrott, 2001). A later meta-analysis reported moderate to large 'effect sizes' for different types of memory deficit, including

short-term and long-term verbal memory (Laws & Kokkalis, 2007). Another comprehensive review noted that the retrospective memory deficits of abstinent Ecstasy users were significant in comparison with both non-user controls and polydrug user controls (Rogers et al., 2009). The complex mixture of deficits on some cognitive tasks and normal performance with other cognitive functions has been noted in many papers and reviews (McCann et al., 1999; Parrott, 2001, 2006, 2013a, 2013b; Burgess et al., 2011; Rogers et al., 2009; McCann & Ricaurte, 2014; Roberts et al., 2017). Many of the neurocognitive and related problems of MDMA users are also similar in some ways to those caused by other recreational drugs, such as amphetamine or cocaine (Table 15.3; Parrott et al., 2011). So that while retrospective memory deficits are found in 'relatively pure' MDMA users, the memory problems may be worsened by additional drug usage (Mohamed et al., 2011; Wunderli et al., 2017).

Another key type of memory is prospective memory, for instance, remembering to meet someone at a prearranged time and place—in the future. This more complex aspect of memory involves cognitive and temporal planning and seems even more sensitive to the damaging effects of recreational Ecstasy/MDMA (Parrott, 2013a,b). The first report of prospective memory deficits (Hefferman et al., 2001) has been confirmed using a wide variety of task paradigms (review: Parrott, 2013b). The extent of these deficits increases with greater lifetime usage (Rendell et al., 2007), and many recreational Ecstasy/MDMA users report problems with their prospective memory ability (Rodgers et al., 2003). One study employed a virtual reality task that modelled the multiple daily tasks of an office worker; the significant deficits of the Ecstasy users were attributed to problems in memory and task organization (Montgomery et al., 2010). Simple problem-solving skills are also impaired in drug-free MDMA users (review: Parrott, 2013b). Fox et al. (2001) found that performance on a problem-solving task was 250% slower in heavy users, with light and moderate users being cognitively impaired to lesser extents. With the Cambridge Neurocognitive Test Battery (CANTAB), the cognitive profiles of drug-free Ecstasy/MDMA users were found to be similar to those of clinical patients with brain damage to the temporal lobes (Fox et al., 2002).

Deficits have been found in a wide range of higher cognitive tasks, and they are accompanied by significant reductions in social intelligence (Reay, Hamilton, Kennedy, & Scholey, 2006).

In relation to neurocognitive therapy, Spatt et al. (1997) described a 'pure amnesic syndrome' in a 26-year-old female who had taken Ecstasy/MDMA at a rave with adverse consequences. Three days afterward, her performance on standard memory tests was below the fifth percentile, while an MRI scan revealed 'bilateral hyperintense lesions in the globus pallidus'. Occupational therapy as an outpatient was provided for several months, but this was not able to improve her memory problems, and nine months later, her objective memory task performance remained impaired. On the positive side, she 'learned to make extensive use of a diary and a timetable', although she had not been able to return to her previous employment. This degree of memory impairment may be extreme, but many users note that their neurocognitive skills are impaired (Fox et al., 2001, 2002; Parrott, 2000). These cognitive impairments are often accompanied by deficits in other skills, such as visual information processing and psychomotor ability. These diverse impairments can have adverse implications for many daily activities and professional occupations; for an overview and debate, see the final section in Parrott (2013b).

Many drug problems are resolved by abstinence, which leads to the question of whether quitting Ecstasy/MDMA will restore normal cognitive functioning. While some degree of functional recovery might be expected, the empirical evidence on this question is not hopeful. Morgan et al. (2002) found that the Rivermead paragraph memory test scores of former Ecstasy/MDMA users, who had quit for a mean of two years, were around 50% of the scores of never-user controls. Zakzanis and Campbell (2006) found mixed evidence, with some indications of recovery and other indications of enduring memory deficits. Taurah et al. (2013) found that general memory, verbal memory, visual memory, and delayed memory were all significantly impaired in current MDMA users compared to polydrug controls and that former MDMA users displayed enduring deficits on these same tasks. Crucially they found no indications of cognitive skills being restored, despite an average of four

to five years of abstinence. Soar, Parrott, and Turner (2004) described a case study of severe cognitive deficits seven years after quitting.

Table 15.3 Neurocognitive Performance and Self-Rated Moods in Recreational Cocaine and Ecstasy/MDMA Users: Comparative Effects from Three Co-Studies (after: Parrott et al., 2011).

Study 1: L. Evans. Memory and Cognition	Control Group	Cocaine/MDMA	MDMA
Dysexecutive Questionnaire (problem score)	22.1	38.2***	37.1**
Consonant updating (correct recall)	3.2	3.1	2.1
Random letter (number generated—two/seconds)	98.1	83.1***	96.6
Supraspan word recall (total words)	31.1	29.9	27.9
Study 2: J. Howell. Mood States On-Drug and Post-Drug Recovery	Control/Alcohol	Cocaine	MDMA
Excitement (on-drug)	3.6	4.0	4.7*
Paranoia (on-drug)	1.5	3.0*	2.5
Clearheaded (on-drug)	3.0	3.1	1.8*
Aggression (on-drug)	2.3	3.1	1.5

Over-heated (on-drug)	2.5	3.5*	3.9**
Depressed (post-drug recovery)	2.1'	2.7	3.2*
Paranoia (post-drug recovery)	1.6	2.6*	3.6***
Sociable (post-drug recovery)	3.7	3.1	2.3**
Clearheaded (post-drug recovery)	3.8	3.3	2.1**
Study 3: R. Robart. Memory and Cognition	Control Group	Cocaine	MDMA
Rivermead Behavioural Memory (info recalled)	9.9	9.2	8.9
Auditory Verbal Learning task (words learned)	9.4	8.0	7.2*
Trail Making (task completion time)	15.9	19.9	21.4**

Tukey paired comparison tests with control group (two-tailed):

\*  $p < 0.05$  \*\* $p < 0.01$  \*\*\*  $p < 0.001$

## Sleep

MDMA can alter sleep patterns, both acutely and chronically. Jones, Callan, Blagrove, and Parrott (2008) described the patterns of self-reported sleep after weekend Ecstasy/MDMA. They noted significant

reductions in sleep time and sleep quality for several days afterward, with sleep patterns returning to normal after five or six days. In relation to chronic sleep effects in abstinent users, Allen, McCann, and Ricaurte (1993) found a reduction in total sleep time, due mainly to less stage 2 non-REM sleep. In a review, McCann and Ricaurte (2007) concluded that abstinent Ecstasy/MDMA users were at increased risk for chronic sleep disturbances. In a later study, McCann et al. (2009) revealed the medical disorder 'sleep apnoea' in young recreational users, with incidence rates related to lifetime MDMA usage. The authors noted that serotonin was important in the control of breathing and hypothesized that this particular sleep disorder might be another reflection of serotonergic neurotoxicity. Ogeil et al. (2013) noted that around 70% of Ecstasy/MDMA users reported sleep disturbances. In relation to therapy, it is recommended not to administer sleep medications, since they all tend to be problematic when used chronically, because of tolerance or withdrawal problems. The best advice is abstinence—in the hope that sleep may gradually improve, although the limited evidence suggests that this disorder can be enduring (Taurah et al., 2013) and may possibly be permanent.

### **Dental Problems**

In the first empirical investigation of recreational MDMA users at a Californian university, Peroutka et al. (1988) reported that the main psychophysiological effects of a typical dose of 125mg MDMA were tachycardia or increased heart rate, trismus or jaw clenching, and bruxism or tooth grinding. Most recreational users see these feelings of tight jaw, clenched teeth, grinding of the molars, and compulsive chewing as normal hazards. Indeed, some users take these physiological-psychomotor effects, along with other aspects of the serotonin syndrome, as indications that they have been sold genuine MDMA (Parrott, 2002). Tooth grinding and compulsive chewing can, however, cause dental problems. Nugent et al. (2017) described the case of an 18-year-old female, who presented for emergency medical treatment with extensive tissue loss to her lower lip. An accompanying friend reported that following MDMA, the patient demonstrated 'involuntary chewing of her lower lip. Despite the pain, this persisted for

several hours'. This chewing caused a 3 cm loss of tissue in the lower lip and the tissue below it. Facial surgery attempted to join the remaining skin and jaw tissues together, although 'no oral seal was achievable'; the photograph in the dental journal shows the remaining hole beneath the mouth and surrounding lip disfigurement. Kalant (2001) noted that bruxism was generally limited to the period of acute drug action, although in some MDMA users, the compulsive chewing and grinding persisted afterward. Chronic dental problems are thus a practical hazard for some MDMA users, with worn-down back molars being the main problem (Redfearn et al., 1998).

### **Neonatal Problems**

Many psychoactive drugs can damage foetal development, and MDMA is no exception. McElhatton, Bateman, Evans, Pughe, and Thomas (1999) found that mothers who had used MDMA during pregnancy had children with an increased rate of congenital defects. These anomalies predominantly occurred in the cardiovascular and musculoskeletal systems. In a prospective investigation, the Drugs and Infancy Study (DAISY) monitored 28 mothers who took Ecstasy/MDMA during the first trimester of pregnancy (Moore et al., 2010). The control group comprised 68 mothers who had used other recreational drugs, legal and/or illicit, during their pregnancy and included several with Ecstasy/MDMA experience. The neonates and new mothers were prospectively assessed on a battery of psychological tests on several occasions. One heavily MDMA-exposed mother gave birth to a neonate with some congenital defects, a problem not found in the other groups. With the group comparisons, the more heavily MDMA-exposed neonates had significantly lower 'motor quality' scores at four months post-partum (Singer, Moore, Fulton et al., 2012), and these psychomotor deficits remained significant at the 12- and 24-month post-partum sessions (Singer, Moore, Min et al., 2012; Singer et al., 2015). These findings need to be replicated, and the effects of MDMA on male sperm need to be studied. In relation to practical advice, all women should be advised to be drug-free for one month before planning a pregnancy. This advice should also be given to all men.

## Final Overview

The use of MDMA leads to a wide range of acute and chronic problems (Tables 15.1 and 15.2). Furthermore, it has taken years of painstaking empirical research to reveal the multitude of these psychobiological deficits (Parrott, 2013a, 2013b). This has worrying implications for the many novel psychoactive substances now becoming available to illicit drug users (UNODC, 2018). Many of these new drugs will be damaging in ways both similar to, and dissimilar from, the more established drugs, such as cocaine, methamphetamine, or MDMA (Parrott, 2015). So that while some of the NPS-induced problems may be predictable, others may be more esoteric and difficult to understand. This makes it increasingly difficult for the physicians working in emergency medical centres. In relation to therapy, currently the empirical evidence for MDMA is very limited. The only area with good practical advice is the treatment of acute medical problems. Physicians and medics in hospital emergency departments have developed standard procedures for reversing acute hyperthermia by rapid cooling and reversing acute hyponatraemia by the immediate restoration of normal sodium levels (Table 15.1). Both disorders can be fatal when not treated rapidly, hence many thousands of lives have been saved by hospital physicians and medical staff. Other current medical treatments include liver transplantation following acute liver failure and blood transfusions with platelets for uncontrollable bleeding.

Yet acute deaths from MDMA are currently increasing because of three main factors: higher dosage levels, the failure to bring casualties into hospital soon enough, and the increasing use of NPS co-drugs with unknown pharmacodynamics.

The regular use of MDMA can lead to a range of chronic problems, caused by repetitive damage to the neurohormonal and neurotransmitter systems (Table 15.2). Currently, there is minimal knowledge about any effective therapies. Indeed, current limited knowledge suggests that much of the chronic damage caused by MDMA may be enduring (Taurah et al., 2013). Chronic deficits occur in a wide range of psychobiological functions: memory, problem-solving ability, some visual skills, psychomotor integrity, sleep, homeostasis,



immunocompetence, and other areas (Parrott, 2013b). Severe consequences can occur after a single MDMA dose (Spatt et al., 1997) or following chronic repeated doses (Jansen, 1999; Soar et al., 2004). The typical user displays a moderate degree of impairment but one that is not disabling. For instance, 70% of MDMA users report sleep impairments—yet they can still sleep. Memory problems are reported by most regular users (Parrott et al., 2006), yet basic memory functions are retained (Fox et al., 2002; Kish et al., 2010). Problem-solving ability and social intelligence are reduced but are not completely lost (Reay et al., 2006). For many of these functions, heavy users are more impaired than light users (Fox et al., 2001; Rendell et al., 2007).

Hence an important piece of practical advice for light users is to stop taking any more—in order to minimize the further development of any structural brain damage or functional deficits (Parrott, 2015). The various psychiatric problems caused by MDMA, such as depression, often seem to be reversed by abstinence (Turner et al., 2014). However current evidence suggests that neurocognitive functions may remain impaired over time (Taurah et al., 2014). Hence therapies should teach new life skills, such as note taking to cope with memory impairments, and social skills retraining to reverse the decline in social intelligence. In severe instances, retraining for simpler occupations or employments may be necessary (Spatt et al., 1997). In a debate of the potential implications of all these functional deficits, it was suggested that many everyday skills and occupational abilities could be impaired by regular MDMA usage (Parrott, 2013a, b). Hence the best practical advice is to reduce its usage entirely. In particular, we need to reverse the very misleading message that MDMA is safe for human consumption.

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