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Review

MDMA: Interactions with other psychoactive drugs

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ABSTRACT

3,4-Methylenedioxymethamphetamine (MDMA, ecstasy) is one of the most widely abused illegal drugs. Some users self-report euphoria and an increased perception and feeling of closeness to others. When taken in warm environments, MDMA users may develop acute complications with potential fatal consequences. In rodents, MDMA increases locomotor activity and, depending on ambient temperature, may produce a dose-dependent, potentially lethal hyperthermia. Like most other recreational drugs, MDMA is frequently taken in combination with other substances including tobacco, EtOH, marijuana, amphetamines, cocaine and, caffeine. Although polydrug use is very common, the understanding of the effects of this multiple substance use, as well as the analysis of consequences of different drug–drug associations, received rather little attention. The purpose of this review is to summarize our current knowledge about the changes on MDMA-related behavior, pharmacology, and neurotoxicity associated with co-consumption of other drugs of abuse and psychoactive agents.

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1. Introduction

1.1. MDMA epidemiology

In Western countries, a large number of young people consume the amphetamine derivative, (±)-3-4 Methylenedioxymethamphetamine (MDMA), better known as ecstasy, at clubs, "raves", and such other venues (Gross, 2002; Hopfer et al., 2006; Schifano, 2004; Ter Bogt and Engels, 2005). As estimated by the United Nations, the number of "MDMA"-group users ranges between 10.5 and 25.8 million people worldwide, i.e. 0.2% to 0.6% of the population between the ages of 15 and 64 (United Nations Office on Drugs and Crime - UNODC, 2010). The estimated annual rate of MDMA use for that demographic is 1.2% in Western and Central Europe and 0.9% in North America (UNODC, 2010). The 2009 National Survey on Drug Use and Health reported usage among adolescents aged 12–17 years at 1.4%, among adults aged 18 to 25 at 3.9%, and for adults aged 26 and older, 0.3% (NSDUH, 2010). Wish et al. (2006) reported that about 9% of American East coast college students had taken MDMA at least once. According to the Drug Enforcement Administration, there was just one MDMA-related death in the US in 1994; by 2001, the mid-year estimate was 76 (DEA, 2001). Most of MDMA-related deaths occur in individuals in their early teens to mid-20s and who are from middle and upper middle class families (DEA, 2001). In the United Kingdom, where about 4.5% of young adults aged 15–34 years have taken MDMA on at least one occasion in the previous 12 months (Hall and Henry, 2006), Schifano et al. (2006) reported 394 related fatalities between 1994 and 2003. In 42% of these cases, the cause of death was MDMA alone; in all other cases, co-factors contributed. In 2002, MDMA represented slightly more than 4% of the drug-related fatalities documented in the United Kingdom.

1.2. MDMA: Purity and polydrug use

MDMA is almost always consumed orally in the form of tablets (Cole and Sumnall, 2003). One important factor in MDMA use is the purity of street-grade tablets. In fact, the impurities may pose a risk for the users' health including anxiety, mood and possible psychotic disorders (Tanner-Smith, 2006). Not surprisingly, MDMA tablets delivered on the street may contain substances other than MDMA, including other methamphetamines (Parrott, 2004a), ephedrine, caffeine, and ketamine (Makino et al., 2003). Therefore, the purity of MDMA tablets, in terms of MDMA content, is variable (Cole et al., 2002; Parrott, 2004a). Importantly, most MDMA users worldwide are also polydrug users, frequently combining MDMA with drugs such as EtOH, amphetamines, hallucinogens and cannabis (Scholey et al., 2004; Winstock et al., 2001). Wu et al. (2006) reported the prevalence of club drug use in a sample of American youths. Among 16- to 23-year olds, 14% reported using MDMA, 13% LSD, 5% methamphetamine, 0.4% ketamine, 0.4% flunitrazepam, and 0.05% gamma-hydroxybutyric acid (GHB). MDMA related lethal effects may be caused by other ingredients within MDMA pills or by co-consumption of other drugs. For instance, in Australia, 82 MDMA-related deaths were reported between 2000 and 2005 (Kaye et al., 2009). More than 80% of those were the direct consequence of drug toxicity, but in almost 60% cases, MDMA was associated with at least one other drug, predominantly methamphetamine, morphine, and EtOH.

2. Pharmacology of MDMA

2.1. MDMA acute effects

In humans, the most salient acute effects of MDMA are mood-enhancement, increased energy, empathy and, euphoria (Hall and Henry, 2006; Kolbrich et al., 2008). Alternatively, MDMA may produce a number of serious side-effects such as disruption of thermoregulation, tachycardia, hypertension, seizures, and intracranial hemorrhage (Green et al., 2003; Kolbrich et al., 2008). Indeed, some adverse MDMA effects may be life-threatening. These include rhabdomyolysis, hyponatremia, disseminated intravenous coagulation, and acute renal failure (Ben-Abraham et al., 2003; Devlin and Henry, 2008; Henry et al., 1992). More precisely, MDMA disrupts thermoregulation and thus, should be considered to be poikilothermic (Rusyniak et al., 2008; for a review on thermoregulation see Docherty and Green, 2010). Other adverse acute effects of MDMA are altered immune function and increased susceptibility to infectious diseases in rats (Connor et al., 1998; Connor, 2004) and humans (Pacifici et al., 2002), and hepatotoxicity in rats (e.g., Beitia et al., 2000; Carvalho et al., 2004). There are many interspecies similarities and differences in terms of the physiological, behavioral and toxicological effects of MDMA based on both pharmacokinetic and pharmacodynamic peculiarities (see, for example, De la Torre and Farre, 2004; Easton and Marsden, 2006). Comparatively, MDMA produces acute hyperthermia in mice (Fantegrossi et al., 2003), rats (Brown and Kiyatkin, 2004), guinea pigs (Saadat et al., 2004), pigs (Fiege et al., 2003; Rosa-Neto et al., 2004), rabbits (Pedersen and Blessing, 2001), non human primates (Taffe et al., 2006; Von Huben et al., 2007), and humans (Freedman et al., 2005). It is noteworthy that rats kept in a high ambient temperature show augmented MDMA-induced hyperthermia (Mechan et al., 2001), whereas in humans, MDMA has been reported to produce hyperthermia regardless of ambient temperature (Freedman et al., 2005). As reported by these authors, the subjects were administered MDMA at an ambient temperature of 23 °C and then one group had the temperature changed to 18 °C (cold condition) and another group had the temperature changed to 30 °C (warm condition). Alternatively, Von Huben et al. (2007) showed that at 18 °C rhesus monkeys showed hypothermia. It may be that in humans, 18 °C is insufficient to produce hypothermia. What about the MDMA-intoxicated partygoer who attends a rave at 30 °C and then walks home in 0 °C weather?

2.2. MDMA reward and reinforcement

Across species, MDMA produces a unique neuropharmacological profile, including increased synaptic concentrations of serotonin (5-HT), dopamine (DA), and norepinephrine (Rothman et al., 2001). Furthermore, other neurotransmitters affected by MDMA include gamma-amino butyric acid (GABA) (Bankson and Yamamoto, 2004; Simantov and Peng, 2004) and acetylcholine (Fischer et al., 2000; Nair and Gudelsky, 2006; Riegert et al., 2008). Investigators have shown that MDMA increases DA in the nucleus accumbens (Bilsky et al., 1998; Cadoni et al., 2005; Daniela et al., 2004). There is evidence to suggest that both D1-like and D2-like receptors maintain MDMA-self administration in rats (Brennan et al., 2009). Furthermore, the D1 receptor antagonist SCH23390 (Daniela et al., 2004) and D2 receptor antagonist eticlopride (Brennan et al., 2009) attenuate MDMA-induced drug seeking behavior in rats (Schenk et al., 2011). In addition, there is evidence indicating that A2a adenosine receptors modulate the reinforcing efficacy of MDMA as evident from the abolishment of MDMA self-administration in A2a knockout mice (Ruiz-Medina et al., 2011).

Despite the increase in nucleus accumbens DA, the rewarding effects of MDMA are inconsistent. For example, MDMA (0.5, 2 and 4 mg/kg) reduces the responding rate for intracerebral self-stimulation (ICSS) in the nucleus accumbens in rats, an effect opposite to that of cocaine and D-amphetamine (Lin et al., 1997). Some animals continue to respond however, which indicates individual differences in this effect. Hubner et al. (1988) found that MDMA lowers the reward threshold in a dose-dependent fashion for ICSS in the medial forebrain bundle in rats. Hence, they suggest that the reward effect of MDMA is similar to that of other abused substances. The differences between the two findings may reflect regional differences and/or differences in subjective effects of each drug; D-amphetamine is able to substitute for MDMA; however, the reverse is not true (Oberlender and Nichols, 1988).

There is a growing literature on the rewarding effects of MDMA, including MDMA self-administration in laboratory primates and rodents (Reveron et al., 2010; Schenk, 2009; Wang and Woolverton, 2007). MDMA has been reported to be self-administered intravenously by about 60% of naïve rats, a proportion much lower than what is usually reported for cocaine or amphetamine (Schenk et al., 2007). In addition, there is evidence to suggest that the interoceptive stimuli produced by MDMA in rats differ from those produced by cocaine and other psychostimulants as well (Ratzenboeck et al., 2001). Recently, Ben Hamida et al. (2008) demonstrated that in rats the pattern of locomotor stimulation and sensitization produced by MDMA is different from that produced by amphetamine or cocaine. Nonetheless, there is some evidence showing that under certain conditions (e.g., delivery of MDMA associated with a light cue or self-administration under increased ambient temperature), MDMA may produce long-lasting rewarding effects and may thus lead to compulsive use (Cornish et al., 2003; Daniela et al., 2004; 2006; Daza-Losada et al., 2007). Moreover, a priming injection of MDMA in rats (10.0 mg/kg, i.p.) produced drug seeking behavior which is influenced by initial sensitivity to the reinforcing effects of MDMA (Colussi-Mas et al., 2010).

Intravenous self-administration of MDMA has also been demonstrated in monkeys (Lile et al., 2005; McClung et al., 2010) and mice (Orejarena et al., 2009; Trigo et al., 2006); however, compared to cocaine self-administration, monkeys administer fewer doses and show a lower break-point, the highest response requirement completed by the animal under progressive ratio schedule of reinforcement (Lile et al., 2005). Rewarding effects of MDMA as measured by conditioned place preference (CPP) have been demonstrated in rats (Bilsky et al., 1998) and mice (Robledo et al., 2004; Salzmann et al., 2003). MDMA CPP, however, depends on both dosage and protocol (Bilsky et al., 1998). For example, Jones et al. (2010) showed no CPP in rats at a dose of 6.6 mg/kg. Also, some investigators have suggested that there is a difference between the MDMA responses of primates and rodents. In rhesus monkeys, MDMA does not increase locomotor activity (Taffe et al., 2006) in contrast to what is usually observed in rats (Easton and Marsden, 2006). Furthermore, in rats, self-administration of MDMA (3.0 mg/kg, i.v.) causes gradual and significant increases in MDMA intake and MDMA-induced hyperlocomotion (Reveron et al., 2010). It is interesting to highlight that adolescent exposure to MDMA (5 mg/kg) increased the duration of the conditioned rewarding effects of MDMA. Therefore, MDMA exposure during adolescence prolongs MDMA rewarding effects (Ribeiro Do Couto et al., 2011).

2.3. MDMA long-term effects: Neurotoxicity

There is evidence from PET scans and SPECT scans to suggest that MDMA may reduce brain serotonin transporter densities in humans (Cowan et al., 2008; Kish et al., 2010; Reneman et al., 2006; Semple et al., 1999). Additionally, long-term use may produce a number of psychiatric disorders, including impaired impulse control, neuroticism, and psychotic episodes (Morgan et al., 2002). High doses of MDMA (e.g., 10–20 mg/kg) deplete 5-HT, an effect that may persist for up to one year in rats (e.g., Battaglia et al., 1988; Lew et al., 1996) and for several years in primates (e.g., Easton and Marsden, 2006). Such depletion has been interpreted primarily as reflecting serotonergic toxicity (Green et al., 2003), although this view is not shared by all (Baumann et al., 2007; Wang et al., 2004). Moreover, the type of neurotoxicity may be species-dependent. For instance, in mice, MDMA produces neuronal loss, but the toxicity is limited to dopaminergic neurons (Granado et al., 2008a, b; Xie et al., 2004). Several hypotheses have been advanced to explain this differential toxicity in rats and mice. It is postulated that MDMA metabolism is similar qualitatively in most animal species and humans, but may differ in mice. In fact, in mice, MDMA causes DA release which can be oxidized to neurotoxic, reactive oxygen species (ROS) (de la Torre and Farre, 2004). Furthermore, the toxicity in mice may be attributed to MDMA metabolites rather than to the drug itself (Escobedo et al., 2005). In other species, including humans, the most widely cited basis for MDMA-induced neurotoxicity is via its metabolites. These are reported to contribute to ROS formation with selective neurotoxicity to 5-HT neurons (de la Torre and Farre, 2004; Sprague and Nichols, 2005).

To summarize, the mechanisms by which MDMA induces neurotoxic effects remain controversial. MDMA-induced release of 5-HT via the serotonin transporter (SERT) is the most accepted theory to explain MDMA-induced neurotoxicity. Nonetheless, MDMA effects on various brain neurons are species-dependent. Furthermore, the rank of the affinity of MDMA for human transporters is different from what is observed in rats, with the highest affinity for the norepinephrine transporter followed by SERT and the dopamine transporter (DAT) (Verrico et al., 2007). It is noteworthy that dose and dosing regimen affect the severity of MDMA-induced long-term effects. Within this context, in rats, repeated sub-chronic treatment with MDMA, i.e. 20 mg/kg/day for ten consecutive days, decreases noradrenaline and/or serotonin release with the augmentation of DA release within the nucleus accumbens (Mayerhofer et al., 2001). Other putative mechanisms for MDMA-induced neurotoxicity include metabolic toxic products, oxidative stress, hyperthermia, apoptosis, and carrier-dependent transport of MDMA (Green et al., 2003; Sanchez et al., 2001; Shankaran et al., 1999; Simantov and Tauber, 1997).

2.4. Teratogenic and perinatal effects of MDMA

MDMA can pass the placental barrier (Campbell et al., 2006; Williams et al., 2004) and is a putative teratogen (Draper et al., 2008;

McElhatton et al., 1997; 1999). Human exposure in utero is related to increased risk for club foot and congenital heart defects (McElhatton et al., 1997; 1999). Indeed, there is a growing literature on pre- and perinatal effects of MDMA in animals (Piper, 2007; Skelton et al., 2008). Heuland et al. (2010) showed that *in utero* exposure to MDMA in Wistar rats between the 13th and 20th days of gestation (corresponding to the beginning and middle of the second trimester of human pregnancy) delays postnatal physical (eye opening and incisor eruption), neurological (hindlimb grasp) development and retards sensorimotor development (gait reflex and inclined board performance). Furthermore, rats exposed to MDMA *in utero* showed a two-fold decrease in brain 5-HT concentration at birth (Galineau et al., 2005) and a decrease in striatal DA metabolites from postnatal days 3 to 21 (Koprich et al., 2003). Recently, Kaizaki et al. (2010) found that MDMA inhibits Neurite Growth Factor-induced neurite outgrowth. In summary, MDMA is a likely teratogen in animals as well as in humans. One putative mechanism is DNA damage (Alvarenga et al., 2010; Barenys et al., 2009; Fornai et al., 2004), even at relatively low doses (Frenzilli et al., 2007). These studies point to the need for increased awareness about MDMA as a potent teratogen.

3. MDMA + EtOH

Because EtOH is legal, readily available, and consumed at many social events in Western countries, it is frequently combined with MDMA (Barrett et al., 2005; Lora-Tamayo et al., 2004). A large number of articles report co-abuse (see Barrett et al., 2006; Breen et al., 2006; Lora-Tamayo et al., 2004; Riley et al., 2001; Winstock et al., 2001). Evidence from clinical studies suggests that ingestion of EtOH before cocaine, D-amphetamine, or MDMA increases plasma concentration of these drugs (Cami et al., 1998; Perez-Reyes et al., 1992; Oesterheld et al., 2004). Effects of EtOH on MDMA may depend on several factors including interval between dosing, EtOH dose, and ambient temperature.

3.1. MDMA + EtOH in humans

In humans, EtOH prolongs the euphoric effects of MDMA with dissociation between subjective and objective sedation (Hernandez-Lopez et al., 2002). Dumont et al. (2010a) recently found that subjects intoxicated with both substances combined were more alert as compared to placebo, although their psychomotor accuracy was significantly impaired. Moreover, Dumont et al. (2010b) found that the co-intoxication did not affect cardiovascular function as compared to MDMA alone, but lessened the effect of MDMA on fluid retention and tended to attenuate MDMA-induced hyperthermia. In an earlier study, Dumont et al. (2008) reported that in humans, MDMA + EtOH has no effects on executive, memory, psychomotor, visuomotor, visuospatial or attention function, or on subjective experience. According to Cassel et al. (2008), the authors may have missed an effect, as they used a lower dose of EtOH compared to what is observed when humans take MDMA + EtOH (Dumont et al., 2008). Hernandez-Lopez et al. (2002) reported that MDMA + EtOH prolongs the duration of euphoria and feeling of well-being compared to EtOH or MDMA alone. Kuypers et al. (2006) and Ramaekers and Kuypers (2006) investigated the effects of MDMA + EtOH on actual driving performance and laboratory tasks related to driving in a placebo-controlled study. They found that MDMA reduces weaving in road tracking test. In contrast, EtOH alone increases weaving and impairs brake reaction time and coherence. Moreover, MDMA tends to ameliorate the EtOH-induced weaving increase. Car-following is impaired by EtOH alone and in combination with MDMA. Reaction time for braking is also impaired and made worse by MDMA. Moreover, MDMA has no effect on EtOH-related impaired judgment. Consequently, MDMA counteracts some, but not all of the EtOH effects on driving.

3.2. MDMA + EtOH in animals

In animals, EtOH has been reported to increase brain MDMA concentration in mice (Johnson et al., 2004) and in plasma and brain of rats (Hamida et al., 2009). EtOH also has been shown to potentiate the hyperlocomotion effect of MDMA in rats and to attenuate its hyperpyretic effects (Ben Hamida et al., 2006; 2008; Cassel et al., 2004; 2005; 2007). In fact, MDMA disrupts thermoregulation (Rusyniak et al., 2008) and should be considered to be poikilothermic as is EtOH. Additionally, the preventive effect of EtOH against MDMA-induced hyperthermia depends on ambient temperature. For instance, such protection is observed at an ambient temperature of 23 °C but not at 32 °C in rats (Cassel et al., 2007). Moreover, with intermittent administration of MDMA and EtOH, like recreational drug usage, there is marked sensitization to the locomotor effect of the combination, which suggests that EtOH modulates some central MDMA-related activity (Ben Hamida et al., 2007). In terms of neurochemistry, Riegert et al. (2008) showed that while MDMA has the expected effect of increasing spontaneous release of 5-HT from rat brain striatal slices, when EtOH is added to the mix, an increase in DA release is observed. Consequently, this may explain why EtOH potentiates hyperlocomotion in MDMA-treated rats. Johnson et al. (2004) demonstrated that EtOH increases striatal d-MDMA levels by 4- to 7-fold in mouse brain. Importantly, in the striatum, we have generated preliminary microdialysis data on a small number of rats suggesting that the MDMA + EtOH produces a larger release of DA than MDMA alone (Ben Hamida et al., unpublished); these results nevertheless require confirmation. Furthermore, Jones et al. (2010) conducted CPP testing for MDMA at 6.6 mg/kg with and without EtOH at 0.75 g/kg. The data showed that animals spend more time in the compartment associated with the combination of both drugs than those associated with saline, EtOH, or MDMA alone. These studies underscore the unique effects of EtOH + MDMA; in humans these include enhanced and prolonged euphoria (Hernandez-Lopez, et al., 2002); while in animals, this combination potentiates the hyperlocomotor effects of MDMA and may enhance its rewarding effect. Of course, the converse may be true that MDMA interacts with the effects of EtOH or the combination itself produces unique effects. In a recent study, Hernandez-Rabaza et al. (2010) administered MDMA and EtOH to adolescent rats. Two weeks post-treatment, these rats were examined for memory, neurogenesis in the dentate gyrus, and neurotoxicity. Only the rats exposed to the MDMA + EtOH showed memory deficits, an observation consistent with the authors' other observation that MDMA + EtOH reduced the number of mature granule neurons in the dentate gyrus.

From these studies, it is clear that the combination of MDMA + EtOH produces a pharmacological profile that may change according to ambient conditions, dose of EtOH, and dosing schedule. For example, MDMA is not known for compulsive use; yet, the addition of EtOH seems to enhance its reward effect. Consequently, EtOH might increase the potential risk for increased individual use of MDMA and thus the possible risk for dependence, addiction, and neurological damage. For more detailed pharmacological information about MDMA/EtOH interactions, see a comprehensive review in Mohamed et al. (2009).

4. MDMA + cannabis

4.1. MDMA + cannabis in humans

Among the many psychoactive chemicals in cannabis, the most active substance is $^{\Delta}$9-trans-tetrahycrocannabinol. Cannabis is probably the most widely used illicit substance in the Western world

(Smart and Ogborne, 2000; Sydow et al., 2001). Additionally, it is one of the drugs most commonly taken with MDMA (Parrott, 2004a; Parrott et al., 2007; Topp et al., 1999). MDMA + cannabis use worldwide is estimated to be 73% to 100% among young people who take MDMA at rave parties (Sala and Braida, 2005). Lora-Tamayo et al. (2004) screened 154 self-confessed designer drug consumers on Ibiza Island. Not surprisingly, among 30 MDMA users, 20 of them have detectable amounts of cannabinoids in their urine. Wish et al. (2006) reported that among the 9% of 1206 American college students surveyed who had taken MDMA, about 98% had a history of using marijuana. This rate confirms the 90–100% range among MDMA users reported in earlier studies (e.g., Schuster et al., 1998; Rodgers, 2000; Winstock et al., 2001). Barrett et al. (2006) reported that 41.7% of subjects who use cannabis also use MDMA simultaneously. Winstock et al. (2001) reported that 82% of young people in a magazine survey use cannabis with MDMA or use it while the effects of MDMA are wearing off.

There may be many reasons for combining both drugs. Indeed, it seems that many people use cannabis to relieve the unpleasant "come-down" effects of MDMA, such as anhedonia, dysphoria, and depression (Parrott et al., 2000; Parrott, 2004b). Interestingly enough, cannabinoids may mask MDMA-induced aggressive behavior and somatic symptoms (Milani et al., 2005). On the other hand, this combination may present many health hazards. For example, regular MDMA + cannabis users evince various psychological problems such as impulsiveness, anxiety, somatic complaints, obsessive compulsive patterns, and psychotic behavior (Daumann et al., 2001; Lamers et al., 2006). In addition, regular MDMA users report certain psychopathologies in the form of interpersonal sensitivity, depression, and paranoid ideation. These symptoms are attributed to their concomitant use of cannabis (Daumann et al., 2004). MDMA + cannabis users also perform poorly on memory tests and exhibit impaired learning, word fluency, and processing speed (Gouzoulis-Mayfrank et al., 2000; Indlekofer et al., 2009; Parrott et al., 1998; Verkes et al., 2001), especially in semantic verbal fluency (De Sola et al., 2008), as compared to MDMA or cannabis users alone. Furthermore, compared to non-ecstasy users and ecstasy-only users, MDMA + cannabis users showed the greatest impairment in several cognitive tasks (Fisk et al., 2006). Comparisons between the two groups, however, did not reveal large differences, and the authors conclude that cannabis use does not reliably protect against MDMA-related cognitive impairment (Fisk et al., 2006). It has been demonstrated that the combination of these two substances produces an additive effect to impair visual perception and self motion perception, leading to impaired performance on driving-related tasks (Rizzo et al., 2003; 2005).

There is evidence that chronic MDMA + cannabis use is associated with long-term alterations in immunological function, leading to increased susceptibility to mild infections and various immune-related disorders (i.e., common colds, acute pharyngitis and sinusitis, and uncomplicated urinary tract infections) (Pacifici et al., 2007). Moreover, chronic co-use may exaggerate MDMA-induced endocrine abnormalities (Gouzoulis-Mayfrank et al., 2002) including increased release of vasopressin (Forsling et al., 2001; Wolff et al., 2006), increased plasma oxytocin (Dumont et al., 2009b; Wolff et al., 2006), and reduced prolactin and cortisol responses to the serotonergic agonist, D-fenfluramine (Gerra et al., 2000). Such endocrine effects might be explained by the indirect dopaminergic and direct cannabinoid receptor actions of cannabis (Gouzoulis-Mayfrank et al., 2002). Dumont et al. (2009a) reported that THC and MDMA produced an additive effect on increasing heart rate, but attenuated MDMA-evoked norepinephrine release. This group also reported that THC delayed but prolonged MDMA-related hyperthermia.

In a recent study, Lansbergen et al. (2011) investigated MDMA + cannabis and MDMA + EtOH on electroencephalogram (EEG) oscillations by monitoring alpha and theta waves. Theta waves are thought to be related to memory function (Duzel et al., 2010) and alpha waves to active inhibition of visual processing (Sauseng et al., 2009). They found increased theta and alpha power after EtOH intake and a reduction in both following MDMA intake compared to placebo. Furthermore, there is no interaction between EtOH and MDMA. On the other hand, they found that MDMA + THC significantly reduced the alpha-2 band whereas each drug alone did not. These researchers also found a significant MDMA + THC interaction in theta and alpha-1 spectra. In this case, the attenuation of both waves following MDMA + THC is less than the attenuation seen for each drug taken alone. Finally Lansbergen et al. (2011) correlated these EEG oscillations with impairment of cognitive performance among MDMA + THC users. It is worth mentioning, that for some studies, one or more of the effects reported for the combination (e.g., reduced mental flexibility, slower decision making) are relatively similar to those reported for people who consume only cannabis and never MDMA (Croft et al., 2001; Lamers et al., 2006; see also Hanson and Luciana, 2010). Finally, Parrott et al. (2007) caution that while THC may protect against some of the deleterious effects of MDMA, there is still a great deal to know about the potential risks about the combination both on the acute and chronic timeframes.

4.2. MDMA + cannabis in animals

There is some evidence that the activation of CB_1 cannabinoid receptors is necessary for the acute rewarding effects of MDMA, as indicated by the failure of CB_1 cannabinoid receptor-1 knockout mice to self-administer MDMA at any of the used doses (Tourino et al., 2007; 2008). Furthermore, Braida and Sala (2002) reported that pre-treatment with a cannabinoid agonist (CP55,940) increases MDMA intracerebroventricular (i.c.v.) self-administration in rats. Moreover, Braida et al. (2005) showed the CB_1 cannabinoid antagonist, SR141716A, to decrease conditioned place preference (CPP) induced by i.c.v. MDMA in rats. These findings are in contrast to those of Robledo et al. (2007), who reported that the combined administration of THC (0.3 mg/kg) and MDMA (3 mg/kg) in mice produces CPP, whereas the same dose of THC (0.3 mg/kg) with a higher dose of MDMA (10 mg/kg) actually decreases CPP. Moreover, administration of MDMA before THC decreased DA in the nucleus accumbens, whereas administration of THC before MDMA had no effect. Thus, depending on how administered, low doses of THC can modify (increase or decrease) MDMA behavioral effects in animals. These results indicate that CB_1 cannabinoid receptors play an important role in acute MDMA effects and in the acquisition of MDMA-self administration. This notion is further supported by Tourino et al. (2008) as they reported that acute MDMA in wild-type mice stimulates locomotor activity, raises body temperature, and produces anxiogenic-like responses, while in CB_1 knockout animals, these effects are weak or absent.

Acutely, THC (1 mg/kg) or MDMA (5 mg/kg) may impair working memory in rats; however, at these doses, MDMA has less effect than THC. Additionally, MDMA + THC produced greater impairment of working memory than either drug alone (Young et al., 2005). Therefore, at these doses, there is a synergistic disruption of working memory. In Wistar rats, THC has been shown to antagonize the locomotor stimulatory effect of MDMA and to offer some protection against its long term anxiogenic-like effects (Morley et al., 2004a). Furthermore, animal studies show the possible neuroendocrine effects of this combination such as elevation of serum prolactin (Fernandez-Ruiz et al., 1997; Rodriguez et al., 1999) and serum aldosterone (Burns et al., 1996).

THC may protect against MDMA toxicity, and this protection may be mediated by CB1 receptor activation and prevention of hyperthermia (Touriño et al., 2010). Moreover, MDMA and cannabis have opposite effects on oxidative stress. In experimental animals, MDMA increases oxidative stress (Green et al., 2003), whereas THC acts as an antioxidant, by attenuating the neurotoxic effects of MDMA (Grundy,

2002; Parrott et al., 2004). Finally, THC reduces MDMA-related hyperlocomotion and anxiety-like responses in mice (Hayakawa et al., 2004; Touriño et al., 2010) and rats (Morley et al., 2004a).

5. MDMA + cocaine

5.1. MDMA + cocaine in humans

In the street vernacular, combining cocaine with MDMA is known as "bumping up" or "cloud mind" (NSDUH, 2010). Survey studies indicate that 46% of MDMA users also use cocaine (Wish et al., 2006). The percentage of MDMA users reporting using cocaine on ten or more occasions is greatest among heavy MDMA users (59%) as compared to novice (16%) and moderate (28%) MDMA users (Scholey et al., 2004).

5.2. MDMA + cocaine in animals

Both drugs share some biochemical effects (i.e., increased synaptic levels of serotonin, dopamine and norepinephrine) (Rothman et al., 2001), although by different actions on the transporters (Han and Gu, 2006). Cocaine blocks DA transporters, whereas MDMA reverses DA transporter action (Bradberry, 2002; Metzger et al., 1998). Others have shown that manipulations that increase 5-HT function decrease cocaine self-administration (Carroll et al., 1990; Glatz et al., 2002; Howell and Byrd, 1995). Furthermore, it has been reported that there is an inverse relationship between psychostimulant potency and binding affinity at the 5-HT transporter (SERT) site (Ritz and Kuhar, 1989). In this context, MDMA may suppress the psychomotor effects of cocaine indirectly, either through increasing DA release in the nucleus accumbens (Cadoni et al., 2005) or by acting on 5-HT_{2C} receptors (Burmeister et al., 2004; Fletcher et al., 2006).

A large number of preclinical studies have examined the behavioral effects of MDMA + cocaine (Aberg et al., 2007; Cole et al., 2003; Horan et al., 2000; Kalivas et al., 1998; Morgan et al., 1997). In rats, repeated treatment with MDMA facilitates subsequent acquisition of intravenous (i.v.) cocaine self-administration (Fletcher et al., 2001). Pre-exposure to MDMA also augments cocaine CPP (Horan et al., 2000). There is evidence suggesting that MDMA + cocaine in animals may antagonize the rewarding effects of one or both drugs. For instance, Diller et al. (2007) reported that in adult rats, cocaine suppresses CPP for MDMA (5 mg/kg, s.c.). When the dose of MDMA is increased to 10 mg/kg, however, cocaine potentiated CPP. Concurrent administration of MDMA (1.5 or 3.0 mg/kg, i.p.) and cocaine (10 or 20 mg/kg, i.p.) in rats produces locomotor activation and enhances dopaminergic responses to a greater extent than administration of either drug alone, indicating a synergistic effect (Panos and Baker, 2010). Moreover, pretreatment with MDMA (5 mg/kg MDMA daily for 7 days) increases cocaine-induced CPP in adolescent rats while decreasing it in adults (Aberg et al., 2007). What is most striking from these findings is that exposure to MDMA during adolescence may pose a greater risk for abuse of MDMA than exposure during adulthood. In mice, exposure to MDMA during adolescence produces long-lasting sensitization to the cocaine reward effects as measured by CPP and inferred from hyperlocomotion induced by cocaine in adulthood (Achat-Mendes et al., 2003). Furthermore, in adolescent mice, acute cocaine combined with MDMA produces an anxiolytic-like profile expressed as an increase in the time spent on the open arms in the elevated plus maze (Daza-Losada et al., 2009). Mice treated with MDMA and cocaine show decreased striatal DA and increased 5-HT in the striatum and cortex 30 min after administration. This effect leads to a dramatic alteration of the behavioral and neurochemical profile of this cocktail as compared to either drug alone. Trigo et al. (2009) trained adult mice to intravenously self-administer cocaine by nosepokes. The animals then underwent extinction to a criterion of low rates of responding equal between the active and inactive holes. Once the low rate of responding was achieved, the animals received an i.p. injection of MDMA or D-amphetamine and were returned to the operant chamber containing cocaine-associated cues. They found that MDMA, but not D-amphetamine was able to reinstate nosepokes in the formerly active hole. This indicates that MDMA, but not D-amphetamine produces some as yet unknown interoceptive cues in common with cocaine.

6. MDMA + other amphetamine derivatives

6.1. Human studies

Methamphetamine (METH, speed, ice, crystal, crank or glass) is a powerful stimulant. It is inexpensive and can be easily made from over-the-counter ingredients (NIDA, 1999). It is noteworthy that the reinforcing, physiological, and subjective effects of MDMA in humans are similar to those of D-amphetamine (Tancer and Johanson, 2003). MDMA + METH use is seen in many cultures (Barrett et al., 2005; United Nations, 2010) and this combination is considered to be a new epidemic worldwide (Koesters et al., 2002; UNODC, 2010). The co-use of METH with MDMA is likely through impurities in ecstasy tablets — either intentionally or accidentally (Barrett et al., 2005). METH induces euphoric effects and increases self-confidence and energy (Hart et al., 2001). Regular use of MDMA + METH has been reported to cause severe long term cognitive, behavioral, and neurological changes (Brecht and von Mayrhauser, 2002; Reneman et al., 2002). From a neurochemical point of view, chronic MDMA + METH use reduces striatal DAT densities compared to MDMA alone (Reneman et al., 2002). MDMA + METH neurotoxicity may be caused by oxidative stress and free radical production via exhaustion of endogenous free-radical scavenging processes (Hanson et al., 2004).

Para-Methoxyamphetamine (PMA) is also one of the most widely used amphetamines. It was recently reported that PMA abuse has risen significantly worldwide, especially in Australia, Europe and North America (Kraner et al., 2001; Ling et al., 2001; Martin, 2001; Voorspoels et al., 2002). PMA is associated with a higher rate of fatal hyperthermia and is reported to be more hallucinogenic than MDMA; this may be due to its 100-fold greater potency as an MAO-A inhibitor than MDMA (Byard et al., 2002; Scorza et al., 1997). The clinical signs of PMA poisoning are similar to those of MDMA, such as agitation, high temperature, rhabdomyolysis, tachycardia, convulsions, and coma (Green et al., 1995; Hegadoren et al., 1999). Acute effects (euphoria, hyperthermia and serotonin syndrome) are due to the action on the 5-HT transporter (SERT) or the dopamine transporter (DAT), leading to the release of serotonin or dopamine (Callaghan et al., 2005). There is evidence to suggest that MDMA + PMA is highly toxic as inferred from three fatal cases involving the combination (Johansen et al., 2003). Likewise, there was a report of six fatalities related to PMA in Australia, wherein MDMA was detected in the blood of two of the six cases (Felgate et al., 1998).

6.2. Animal studies

Similar to what is observed in humans, serotonin syndrome has been reported in animals. The symptoms include hyperthermia, rhabdomyolysis, and hyponatremia, all of which eventually lead to coma and death (Ener et al., 2003) as a result of overstimulation of 5-HT_1 and 5-HT_2 receptors. The hyperthermic effects of PMA in rats may be exacerbated by the inhibition of the rat's tail vasodilatation heat loss mechanism (Blessing et al., 2003). An ambient temperature of 30 °C significantly exacerbates the serotonin syndrome induced by MDMA alone as well as PMA alone (Stanley et al., 2007). Evidence suggests that rats can be trained to discriminate between MDMA and PMA (Goodwin and Baker, 2000). Moreover, this combination can induce functional changes in 5-HT neurotransmission (Pubill et al., 2003).

Laboratory animal research has shown that MDMA might have lasting effects on responses to other stimulant drugs. For example, MDMA pretreatment augments the locomotor stimulant effect of amphetamine in rats (Callaway and Geyer, 1992). Furthermore, Morley et al. (2004b) reported that in rats, pre-exposure to MDMA (5 mg/kg every hour for 4 h on 2 consecutive days) slows the initial acquisition of amphetamine self-administration and promotes amphetamine seeking behavior along with MDMA hyperactivity. Nevertheless, in rats, pretreatment with MDMA dampens self-administration of METH (Clemens et al., 2006). Repeated treatment with MDMA can induce sensitization to its own locomotor effects without cross sensitization to amphetamine or methylphenidate in rats (Modi et al., 2006). Clemens et al. (2004; 2005) found that rats receiving MDMA + METH show decreased social interaction and increased anxiety-like behaviors. Furthermore, rats that are given MDMA + METH show a significant degree of monoamine depletion as compared to either drug alone, indicating possible synergistic neurotoxicity (Clemens et al., 2004). The above studies underscore that MDMA + METH leads to adverse behavioral and neurochemical effects that are greater than those observed with similar doses of each drug administered alone (Clemens et al., 2007).

7. MDMA + nicotine

There is a clear association between tobacco use and substance use disorders. About 70% of people who use tobacco also use other substances (Degenhardt and Hall, 2001). A reported 64% of drug-using university students use MDMA simultaneously with tobacco (Barrett et al., 2006) and that rate jumps to about 90% for all MDMA users among American adolescents (Martins et al., 2008). Cigarette smoke contains several chemicals in addition to nicotine that may lead to free radical formation and oxidative stress. Hence, tobacco smoke may exacerbate the neurotoxic effects of MDMA (Parrott, 2003). There is a complex relationship between nicotine and MDMA; nicotine can alleviate the negative effects of MDMA and vice versa (Parrott et al., 2005). MDMA reduces the irritability and restlessness associated with decreased serum nicotine during cigarette abstinence (Parrott, 1999). From a neurochemical point of view, nicotine diffuses readily into the brain and binds to central nicotinic acetylcholine receptors. Such binding results in the release of a variety of neurotransmitters in the brain (e.g., DA, ACh, GABA, Glu, 5-HT and NE) (Picciotto, 2003), with the most crucial being dopamine. Nicotine releases dopamine in the mesolimbic area, the corpus striatum, and in the frontal cortex. Additionally, nicotine stimulates dopaminergic neurons in the ventral tegmental area of the midbrain and in the shell of the nucleus accumbens leading to nicotine addiction (Dani and De Biasi, 2001; Nestler, 2005). It is therefore hypothesized that nicotine may facilitate dopaminergic response to other reinforcers (Rice and Cragg, 2004; Zhang Sulzer, 2004). This could be the basis for explaining the common co-use of tobacco with MDMA. In spite of that, the dopaminergic effects of nicotine are considered to be relatively weak compared to those produced by amphetamine (Tsukada et al., 2002). It is noteworthy that in rave parties, smoking methamphetamine mixed with tobacco is common which produces pyrolysis products especially N-cyanomethylemethamphetamine (Sekine and Nakahara, 1990). This agent can produce hyperlocomotion in mice similar to that produced by methamphetamine (Kuribara et al., 1996). Moreover, in humans this product is easily metabolized to methamphetamine (Sekine and Nakahara, 1987); therefore, smoking methamphetamine mixed with tobacco might increase the risk for MDMA-induced neurotoxicity. Additionally, methamphetamine promotes the oxidation of tobacco components (Lee et al., 1999), leading to faster absorption and a rapid rewarding effect for nicotine. The combination of MDMA with tobacco laced with METH presents yet another concern. Now we have the potentially dangerous combination of MDMA + METH combined with a third substance, nicotine.

8. MDMA + caffeine

Caffeine (a methylated xanthine) increases DA release in the striatum (Okada et al., 1997) and is an ancient psychostimulant used world-wide. Klingler et al. (2005) analyzed MDMA pills using gas chromatography/mass spectrometry and their findings show that about 10% of all examined pills contain one or more xanthine derivatives. Moreover, energy drinks which usually contain caffeine are commonly consumed with MDMA to reduce drowsiness and fatigue as a part of the rave party scene. Importantly, MDMA has an anti-nociceptive effect (Crisp et al., 1989) and given that caffeine is also used as an analgesic, this may explain the popularity of combining MDMA and caffeine.

In rats, caffeine acts synergistically with MDMA in producing hyperthermia (McNamara et al., 2006). In addition, the combination of caffeine with the MDMA metabolite, methylene-dioxyamphetamine (MDA), produces a long-lasting reduction in 5-HT and its metabolite, 5-hydroxyindoleacetic acid, in multiple regions of the brain. Thus, caffeine facilitates acute and long-term toxicity associated with MDMA and MDA. McNamara et al. (2007) reported that co-administration of caffeine (10 mg/kg) and MDMA (10 mg/kg) to Sprague–Dawley rats produced a profound tachycardia compared to the tachycardia produced by either drug alone. More recently, Vanattou-Saïfoudine et al. (2010a) reported that co-administration of caffeine (10 mg/kg i.p.) augments acute toxicity of MDMA in adult male Sprague–Dawley rats, especially hyperthermia and tachycardia. The biochemical mechanism of such interaction is uncertain; however, some studies suggest that caffeine facilitates MDMA toxicity predominately via dopamine D_1 action (Vanattou-Saïfoudine et al., 2010b). Camarasa et al. (2006) reported that, in mice, administering caffeine (10 mg/kg) prior to MDMA (5 mg/kg) potentiates MDMA-induced locomotor activity (Camarasa et al., 2006). Therefore it has been hypothesized that caffeine blocks adenosine A_2 receptors, thus potentiating the DA release and increasing MDMA-related hyperlocomotion (Camarasa et al., 2006). Moreover, caffeine may act via inhibition of adenosine A_1 receptors to increase MDMA-induced striatal DA release (Vanattou-Saïfoudine et al., 2011).

9. MDMA + other recreational drugs

MDMA is commonly combined with other illicit drugs. According to Scholey et al. (2004), among MDMA users, these include LSD (60%), psilocybin (56%), barbiturates-benzodiazepines (38%), opiates (23%), and solvents (21%). In a sample of pregnant women in Toronto who used MDMA from 1998 to 2000, Ho et al. (2001) found a tendency for MDMA users to also use illicit drugs such as ketamine (9%), gamma-hydroxybutyrate (GHB) (7%), and psilocybin-containing "magic mushrooms" (4%).

9.1. MDMA + gamma-hydroxybutyric acid (GHB)

GHB is an endogenous inhibitory neurotransmitter (Bessman and Fishbein, 1963) synthesized from gamma-amino butyric acid (GABA) (Maitre et al., 2005). GHB is called "liquid ecstasy" or "liquid X", as it produces MDMA-like effects; viz., euphoria dis-inhibition, and increased social affiliation (Doyon, 2001). In humans, GHB, in small amounts, produces relaxation and euphoria (Sumnall et al., 2008) and reduces anxiety while enhancing social interactions (Dean et al., 1997; Nicholson and Balster, 2001). GHB users sometimes combine it with MDMA with possible interactions between both drugs at a neurochemical and neurobehavioral level (Lee and Levounis, 2008; Uys and Niesink, 2005). In humans, GHB reportedly enhances the euphoric effects of MDMA and prevents the MDMA "come-down" after-effect (Uys and Niesink, 2005).

In rats, acute GHB may augment MDMA-induced hyperthermia (van Nieuwenhuijzen and McGregor, 2009). GHB also affects MDMA-

related locomotor hyperactivity. Acutely, GHB reduces this hyperactivity (van Nieuwenhuijzen et al., 2010b); however, repeated treatments produce sensitization to MDMA-related hyperactivity (van Nieuwenhuijzen et al., 2009a). This biphasic effect might be explained on the basis of an initially MDMA hyperactivity opposed by GHB sedation leading to little overall effect on locomotor activity. This apparent sensitization may result as a consequence of the development of tolerance to GHB or sensitization to MDMA, or perhaps both.

MDMA produces acute pro-social effects in rats (Thompson et al., 2007; 2009), which may involve the release of oxytocin (Thompson et al., 2007). Similarly, GHB produces pro-social effects in mice (Navarro et al., 2008) and rats (van Nieuwenhuijzen et al., 2010b) which may also involve oxytocinergic mechanisms (van Nieuwenhuijzen et al., 2009b). Within this context, van Nieuwenhuijzen et al. (2010b) investigated residual effects in rats following repeated treatments with the combination over ten consecutive days. These researchers also found that MDMA + GHB produced MDMA-like deficits in memory and social behavior. Moreover, they reported the absence of GHB withdrawal symptoms after repeated administration of MDMA + GHB.

GHB and MDMA have some effects in common. For example, in laboratory animals, MDMA induces hippocampal dysfunction through oxidative stress (Frenzilli et al., 2007) and serotonergic loss (McGregor et al., 2003; O'Shea et al., 2006). Likewise, in rats, GHB induces oxidative stress in the cortex and hippocampus (Pedraza et al., 2009; Sgaravatti et al., 2007, 2009) leading to widespread neuronal loss in hippocampus (Pedraza et al., 2009) and cognitive deficits similar to those produced by MDMA. MDMA + GHB in rats produces several unique changes in hippocampal protein expression compared to either drug alone (van Nieuwenhuijzen et al., 2010a). Furthermore, in rats, MDMA + GHB produces increased hypothalamic expression of oxytocin and the oxytocin receptor gene, suggesting that this combination induces long term neuro-adaptation in the hypothalamic oxytocin system (van Nieuwenhuijzen et al., 2010b). MDMA + GHB may thus produce persistent changes in brain and behavior.

Neurochemically, animal studies show a reciprocal relationship between MDMA and GHB. For instance, MDMA increases the release of several neurotransmitters including, 5-HT, DA (Riegert et al., 2008), norepinephrine (Rothman et al., 2001), acetylcholine (Fischer et al., 2000; Nair and Gudelsky, 2006), and GABA (Bankson and Yamamoto, 2004; Simantov and Peng, 2004). Alternatively, GHB inhibits DA release (Howard and Banerjee, 2002) by binding to $GABA_B$ receptors on midbrain dopaminergic neurons (Cruz et al., 2004), thus attenuating the MDMA-induced hyperlocomotion. MDMA also induces an acute release of 5-HT followed by temporary depletion of presynaptic 5-HT stores (Brodkin et al., 1993). Alternatively, GHB increases the availability of 5-hydroxytryptophan (the precursor of 5-HT), thus potentiating presynaptic serotonin turnover (Gobaille et al., 2002).

9.2. MDMA + opiates and derivatives

Notably, there is large proportion of heroin users who initially tried it to alleviate the stimulant effects of MDMA (Gervin et al., 1998; 2001). In a pilot study of 46 rehabilitation patients, about 96% had smoked heroin. Moreover, 34% among them used heroin after taking MDMA to ease the "come down" (Gervin et al., 1998). In a parallel study those individuals who also used heroin to ease the "come down" reported taking MDMA more frequently than those who had not (Gervin et al., 2001). This association between heroin and MDMA might be explained by the tendency of opiates to raise serotonin levels which may compensate for the midweek dysphoria following weekend MDMA use (Curran and Travill, 1997). It is possible that the proserotonergic effects of MDMA may be augmented by ingestion of other proserotonergic drugs (e.g. fluoxetine, amphetamine, heroin) (Oesterheld et al., 2004). There is one case report in which the combination of MDMA and heroin was lethal (Gerevich et al., 2000), perhaps via central serotonin syndrome.

It is well documented that various drugs of abuse acting through different neuronal mechanisms affect the activity of endogenous opioid systems. In return, changes in opioid systems may contribute to the abuse potential of different drugs of abuse. For example, naltrindol (delta-opioid antagonist) blocks MDMA enhancement of electrical brain self-stimulation in rats (Reid et al., 1996), naloxone blocks MDMA-induced hyperlocomotion in mice (Compan et al., 2003), and that naltrexone (a long acting opioid antagonist) attenuates MDMA's ability to produce CPP in rats (Bilsky et al., 1991). Furthermore, in rats, a single administration of MDMA (10 mg/kg) increased striatal and nigral concentrations of neurotensin and dynorphin (Johnson et al., 1991). Additionally, injection of a high dose of MDMA (10 mg/kg) increases preprodynorphin gene expression in the rat striatum (Adams et al., 2005). These findings are in agreement with those of Di Benedetto et al. (2006) who found that acute MDMA increased prodynorphin mRNA in the prefrontal cortex and the caudate putamen in the rat brain, whereas repeated MDMA increased prodynorphin mRNA in nucleus accumbens, hypothalamus, and caudate putamen.

Daza-Losada et al. (2008) studied CPP for morphine in adolescent mice and found pre-treatment with MDMA to not affect morphine CPP 3 weeks after MDMA pretreatment (2 injections/day over three consecutive days). After CPP was extinguished, however, it could be reinstated in control animals at a priming dose of 10 mg of morphine, whereas for MDMA-pretreated mice, the priming dose required to reinstate CPP was 5 mg/kg. The authors concluded that peri-adolescent exposure to MDMA may alter the rewarding effects of morphine during adulthood. Hence, MDMA used in adolescence may increase subsequent risk for dependence on other drugs, including morphine.

9.3. MDMA + LSD

D-lysergic acid diethylamine (LSD) is a widely used hallucinogen among adolescents in the US (Golub et al., 2001). The extent of concurrent use of LSD and MDMA is unknown, yet it is common and carries the "street" name "candyflipping" (Schechter, 1998). Few studies have reported the co-use of LSD and MDMA especially at "rave" parties (Miller and Gold, 1994; Millman and Beeder, 1994). This combination is thought to produce a maximal MDMA-like response as reported by Schechter (1998), who found that co-administration of a subthreshold discriminative dose of LSD (0.04 mg/kg) with MDMA (0.15 mg/kg) enhances MDMA stimulus discrimination in Fawn-Hooded rats. Because both drugs stimulate central serotonin, one might expect either additive or synergic effects of the combination; however, there is no preclinical research on the topic.

9.4. MDMA + ketamine

Ketamine ("vitamin K", "super K") is a powerful anesthetic agent with cardio-respiratory stimulatory effects (Jansen, 1993). It also causes psychological dissociation and hallucinations (White et al., 1982). A survey of 100 ketamine users in Australia showed MDMA to be used with ketamine by 71% of the sample (Dillon et al., 2003); however, these researchers did not report the effects of the combination. In mice, pretreatment with ketamine exacerbates MDMA-induced central dopaminergic, but not serotonergic toxicity (Ke et al., 2008).

10. MDMA + psychotherapeutic agents

A typical dose of 1.7 mg/kg MDMA produces a characteristic psychological profile including feelings of well-being, heightened mood, moderate derealization, and slight perceptual changes (Vollenweider et

al., 1998). There are clinical studies on the combination of MDMA and drugs used to treat affective disorders (Copeland et al., 2006), especially selective serotonin reuptake inhibitors (SSRI) (Singh and Catalan, 2000). One questionnaire survey study of 216 adults, who had used MDMA at least once in the previous 6 months, reported concomitant use of antidepressant medication with MDMA to extend the duration of the MDMA "high" (13% surveyed) or as a sleeping aid (4% surveyed) (Copeland et al., 2006).

Tancer and Johanson (2007) investigated the effects of fluoxetine on the subjective and physiological effects of MDMA in humans. They found treatment with fluoxetine (20 mg/day) for 5 days before MDMA treatment to attenuate most MDMA positive subjective effects and to dampen the effects of MDMA on the Hallucinogen Rating Scale (HRS). Generally speaking, MDMA users who also used antidepressants did not experience physical or psychological side-effects as much as those who did not (Copeland et al., 2006). From a clinical perspective, however, clinicians should be cautious in prescribing fluoxetine as an agent to provide protection from MDMA-induced long term neurotoxicity. The reason for that warning is a likely drug–drug interaction between MDMA and fluoxetine.

In animals, SSRIs, such as fluoxetine and citalopram, block MDMA-induced serotonin release (Gudelsky and Nash, 1996; Hekmatpanah and Peroutka, 1990; Schmidt, 1987), but have no effect on MDMA-related hyperlocomotion (Ando et al., 2010). Furthermore, fluoxetine may antagonize the effects of MDMA (Berger et al., 1992), most likely through competitive binding to the 5-HT transporter, thus preventing 5-HT release. MDMA can, however, release 5-HT through its action at the presynaptic vesicular transporter independent of 5-HT transporter binding (Partilla et al., 2006). In rats, fluoxetine pretreatment has been shown to protect against long-term MDMA-induced neurodegeneration and neurotoxicity (Sanchez et al., 2001). This contrasts with the findings of Upreti and Eddington (2008) who found that fluoxetine pretreatment (10 mg/kg i.p. for 4 days) in rat increases the elimination half life for MDMA and MDA, leading to a 1.4 fold increase in the plasma and brain levels of MDMA and 1.5 fold increase in the plasma and brain levels of MDA with increased risk of MDMA toxicity. Accordingly, it was shown that in vitro fluoxetine significantly inhibits MDMA metabolism (Ramamoorthy et al., 2002).

Pretreatment with 40 mg/kg i.v. to healthy volunteers inhibits most of the psychological effects of an oral dose of MDMA (1.5 mg/kg) including reduction in MDMA-induced positive mood, derealization and depersonalization, and thought disorder (Liechti et al., 2000a). Moreover, citalopram pretreatment reduces elevated blood pressure and heart rate usually produced by MDMA (Liechti and Vollenweider, 2000b).

Clozapine and olanzapine are atypical antipsychotic agents that lower body temperature (Blessing et al., 2003). Clozapine reverses MDMA-induced cutaneous vasoconstriction and produces vasodilation (Blessing et al., 2006). Given that adequate cutaneous blood flow is important for protecting humans against MDMA-induced hyperthermia (Bodenham and Mallick, 1996), clozapine and clozapine-like agents might be used to treat MDMA overdoses (Blessing et al., 2006).

Concerns have been raised regarding other psychotherapeutic agents. For instance, pretreatment of healthy volunteers with ketanserin ($5HT_{2A/2C}$ antagonist) reduces MDMA effects on emotional excitability, changes in perception, diastolic pressure, and body temperature (Liechti et al., 2000b). Moreover, when MDMA was given after haloperidol (D_2 antagonist) pretreatment in healthy volunteers, they reported an increase in anxiety accompanied by difficulty in concentration and fatigue (Liechti and Vollenweider, 2000a). Based on the above studies, it is worthwhile to stress that there are a number of issues that need to be addressed before prescribing any psychotherapeutic agents to individuals who use MDMA.

11. Discussion

Table 1 summarizes the major body of work on MDMA-other drug interactions.

Substance use disorders constitute a major problem worldwide, especially among young adults. Furthermore, there is a great tendency for drug users to engage in simultaneous poly-substance use and polydrug use may be the rule rather than exception. Nonetheless, little attention has been paid to understanding the causes of and mechanisms underlying this behavior. A good example is MDMA, whose use combined with other drugs is widespread (e.g. Martins et al., 2005; Wu et al., 2006). The most commonly used combinations involve EtOH, cannabis, stimulants, and hallucinogens. Each of these drugs produces unique acute effects i.e., EtOH promotes euphoria; cannabis fosters geniality; cocaine induces an acute stimulatory rush; amphetamine produces an arousing hit and heroin induces soporific pleasures. Despite a surge in research on MDMA effects, little attention has been paid to understand how MDMA interacts with other drugs of abuse and with therapeutic agents. In this regard, there are three main realms of effects viz. neuro-behavioral, pharmacokinetics and pharmacodynamics.

Neurobehaviorally, MDMA is often co-used with other agents to enhance physiological, social, and psychological experiences. There is also the likely deliberate choice among some MDMA users to co-use another drug to attenuate aversive effects. Polydrug use among peers is another consideration. MDMA research should therefore consider several factors including dose and dosing regimen, and also which of the drugs are used in combination. Increased preclinical research may help us to better understand the basis for combined use, initiation and cessation of use, and long-term behavioral and neurobiological effects of MDMA combined with other agents. Increased epidemiological and other clinical investigations can help us to understand possible behavioral and psychiatric characteristics of individuals that predispose them to polydrug use (Lieb et al., 2002; Martins et al., 2006).

Turning to pharmacokinetics, most of MDMA is demethylenated to 3,4-dihydroxymethamphetamine (DHMA) by cytochrome P450 2D6 (CYP2D6) (Tucker et al., 1994). MDMA has a non-linear pharmacokinetics, i.e. small increases in MDMA doses lead to larger than predicted increases in its blood concentration — volume of distribution estimation (de la Torre et al., 2000). Competitive inhibition of CYP2D6 by other drugs increases MDMA blood concentrations. Examples of these drugs include fluoxetine, paroxetine, cocaine (Ramamoorthy et al., 2002), amphetamine analogues (Wu et al., 1997), and haloperidol metabolites (Shin et al., 2001). There are many allelic variants of CYPD6 and individuals carrying alleles for slow or rapid metabolism exhibit variable blood concentrations of MDMA or its metabolites (Ramamoorthy et al., 2002; Tucker et al., 1994). Therefore, understanding the pharmacogenetics of MDMA is crucial to the understanding of individual differences in its effects, including toxicity (Davison and Parrott, 1997) and interaction with other agents.

In terms of pharmacodynamic drug–drug interactions with MDMA, it is well known that MDMA inhibits reuptake of 5-HT, facilitates serotonin release, and causes release of DA and noradrenaline (Lyles and Cadet, 2003). Therefore, co-administration of other proserotonergic drugs, like amphetamines, cocaine, dextromethorphan and others, may augment the severity of MDMA's serotonin effects (Oesterheld et al., 2004) with increased risk for developing serotonin syndrome (Sternbach, 1991). MDMA use may precede other substance initiation or it might start after other drug initiation as there are many common predisposing factors for initiation of MDMA use as well as for other substances of abuse. Within this context, Martins et al. (2007) analyzed data from 54,573 respondents aged 12–21 about prior drug use. They found that earlier MDMA use was associated significantly with subsequent illegal drug use (marijuana, cocaine and heroin). Alternatively, marijuana, cocaine and heroin consumption

Table 1
Psychobiological effects of MDMA alone and in combination with common drugs of abuse in human and animals.

Drug(s)	Human		Animals	
	Effects	Reference citation	Effects	Reference citation
MDMA alone	Hyperthermia	Freedman et al. (2005)	Hyperthermia	Brown and Kiyatkin (2004), Docherty and Green (2010) and Rusyniak et al. (2008)
	Tachycardia and arrhythmia	Kolbrich et al. (2008)		
	Increased oxidative stress	De la Torre and Farre (2004)	Increased oxidative stress	Frenzilli et al. (2007)
	Impaired impulse control, neuroticism and psychotic episodes	Morgan et al. (2002)	Acute pro-social effects	Thompson et al. (2007, 2009)
	Positive moods, cognitions and beliefs	Kolbrich et al. (2008) and Parrott (2001)		
MDMA + EtOH	Prolonged euphoria and feeling of well being	Hernandez-Lopez et al. (2002)	EtOH potentiates the hyperlocomotion effect of MDMA and attenuates its hyperpyretic effects	Ben Hamida et al. (2006, 2008) and Cassel et al. (2004, 2005, 2007)
	No effects on executive, memory, psychomotor and attention function	Dumont et al. (2008)	Memory deficits and enhancing MDMA reward effects	Hernandez-Rabaza et al. (2010) and Jones et al. (2010)
MDMA + cannabis	Attenuation of MDMA-induced hyperthermia	Fisk et al. (2006)	Attenuation of MDMA-induced hyperthermia	Morley et al. (2004a, 2004b)
	Attenuation of oxidative stress	Parrott (2006)	Attenuation of oxidative stress	Grundy (2002) and Morley et al. (2004a,b)
	Memory deficits	Gouzoulis-Mayfrank et al. (2000) and Indlekofer et al. (2009)	Memory deficits	Young et al. (2005)
	Cannabis relieves the unpleasant "come-down" effects of MDMA	Panos and Baker (2010) and Parrott (2004b)		
MDMA + cocaine	Not addressed		Hyper-locomotion augmentation	Achat-Mendes et al. (2003) and Panos and Baker (2010)
MDMA + Meth/Amph	Severe long term cognitive, behavioral and neurological changes; and increased neurotoxicity	Brecht and von Mayrhauser (2002) and Johansen et al. (2003)	Augments MDMA-induced hyper-locomotion	Callaway and Geyer (1992)
			Decreased social interaction and increased anxiety-like behaviors	Clemens et al. (2004; 2005)
MDMA + nicotine	Nicotine alleviates the negative effects of MDMA and vice versa	Parrott et al. (2005) and Parrott (1999)	Nicotine augments MDMA-reward effects	Rice and Cragg (2004)
MDMA + caffeine	Reduce drowsiness and fatigue as a part of rave party scene	Klingler et al. (2005)	Augmentation of MDMA-induced hyperthermia, hyperlocomotion and neurotoxicity	McNamara et al. (2006), Vanattou-Saïfoudine et al. (2010a) and Camarasa et al. (2006)
MDMA + GHB	GHB enhances the euphoric effects of MDMA and prevents "comedown" after effect	Uys and Niesink (2005)	GHB augments MDMA-induced hyperthermia with reducing its hyperlocomotion effect	van Nieuwenhuijzen and McGregor (2009) and van Nieuwenhuijzen et al. (2010b)
			Memory deficits and altered social behavior	van Nieuwenhuijzen et al. (2010b)
MDMA + opiates	Ease the "come down" of MDMA	Gervin et al. (2001)	MDMA alters the rewarding effects of morphine	Daza-Losada et al. (2008)
MDMA + LSD	Not addressed		Augmentation of MDMA-like response	Schechter (1998)
MDMA + ketamine	Not addressed		Exacerbation of MDMA-induced neurotoxicity	Ke et al. (2008)
MDMA + psychotherapeutics	Citaloprim attenuates MDMA-induced positive mood, tachycardia and hypertension effect	Liechti and Vollenweider (2000a, 2000b) and Liechti et al. (2000a)	No effect on MDMA-related hyperlocomotion	Ando et al. (2010)
	Fluoxetine attenuates most MDMA positive subjective effects and dampens the effects of MDMA on the Hallucinogen Rating Scale (HRS)	Tancer and Johanson (2007)	Fluoxetine antagonizes the effects of MDMA	Berger et al. (1992)
	Clozapine reverses MDMA-induced hyperthermia	Blessing et al. (2006)	Not addressed	

did not predict MDMA use. These authors concluded that prior use of MDMA increased the risk for marijuana, cocaine, and heroin use rather than vice versa. This differential drug usage pattern may have various possible explanations. The simplest one is that it reflects a preference for certain stimulant or hallucinogenic types of drug with acute MDMA producing a mixture with more stimulant effects (Davison and Parrott, 1997). Another possible explanation for such pattern of usage is many regular MDMA users report tolerance to its effects (Parrott, 2005), complaining that the effects have diminished with repeated usage (Parrott, 2001). The latter, if confirmed, might suggest some sort of cross-tolerance between MDMA and other drugs of abuse.

Gateway theory is another possible mechanism explaining MDMA-addiction behavior. Such theory suggests that there is an increase in the drug exposure opportunity, as once an individual had decided to use one drug; he/she can easily use another illicit drug. This theory was supported by Wagner and Anthony (2002) and Wilcox et al. (2002). A "common risk factor" model is another model to explain the co-use of MDMA with other illicit drugs. This model assumes that, the same risk factors that lead people to use MDMA will lead to the use of other illicit drugs (Agrawal et al., 2004). This is in accordance with Pedersen and Skrondal (1999) who found that MDMA use frequently follows the following sequence: EtOH, cigarettes, cannabis, amphetamines, MDMA, and then heroin. Sometimes polydrug consumers use drug combinations to simply optimize MDMA effects; for example, marijuana and opioids are used by MDMA users to alleviate post-MDMA discomfort, while cocaine is co-used with MDMA to augment the MDMA experience (Parrott, 2001, 2006). Lastly, MDMA after effects, which are characterized by lethargy and depression, can be one factor in polydrug use (Parrott et al., 2008).

12. Conclusions

This review highlights the main findings in humans and animals concerning the effects of combining MDMA with recreational and therapeutic drugs. Where possible, one of the aims was to elucidate similarities and differences between investigations in humans and those carried out in animals (see also Easton and Marsden, 2006). Our major question is, does the combined use of MDMA with other agents increase or lessen risks for compulsive use, toxicity or both? The interaction between MDMA and EtOH in rats would seem to bring that point into sharp focus. There is no doubt that MDMA is the most popular rave drug because of its intense euphoric effects and the accompanying myth about its safety. Therefore, to better gage the extent of MDMA use and drug–drug interactions, we must rely on preclinical studies and human case reports from emergency room visits. Such research should provide clear information and, in turn, inform prevention/intervention efforts.

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