review examines the existing literature on a host of entactogenic drugs, which may prove to be useful alternatives in the future, paying particularly close attention to any neurotoxic risks, neuropharmacological mechanism of action and entactogenic commonalities with MDMA. The substances examined derive from the 1,3-benzodioxole, cathinone, benzofuran, aminoindane, indole and amphetamine classes. Several compounds from these classes are identified as potential alternatives to MDMA.

Keywords

Entactogen, empathogen, MDMA, psychotherapy, PTSD

Figure 1. (a) Phenethylamine, (b) MDMA, (c) MDA, (d) MBDB, (e) BDB, (f) MDEA.

BDB: 1-(1,3-benzodioxol-5-yl)-2-butanamine; MBDB: 1-(1,3-benzodioxol-5-yl)-*N*-methyl-2-butanamine; MDA: 3,4-methylenedioxyamphetamine; MDEA: 3,4-methylenedioxy-N-ethyl-amphetamine; MDMA: 3,4-methylenedioxy-N-methylamphetamine.

Since the mid 2000s, however, there has been a resurgence of interest in MDMA as a medicine to treat various conditions. Considerable research concerning its pharmacological effects and efficacy as a tool in psychotherapy, including several clinical studies in human volunteers, has been conducted recently (Danforth et al., 2018; de la

respond adequately to the typical clinical dose employed in such a setting and may require larger, and potentially dangerously high, doses of this compound to benefit from the psychological effects. These patients could instead receive compounds that do not produce cross tolerance with MDMA. On the other hand, very sensitive patients may be overwhelmed by the psychotropic effects of a full dose of MDMA, and may benefit from receiving a milder, or shorter-acting entactogen first, to allow them to gently get acquainted with an MDMA-like experience before receiving a therapeutic dose of MDMA. Finally, it is clearly desirable to give medical practitioners as large a pallet of pharmacological tools as possible, to enable them to customise therapeutic sessions to each patient's individual needs, in order to maximise therapeutic progress. It is therefore

problems associated with including elderly individuals and those with a prior history of heart disease in clinical studies (Bershad et al., 2019; Doss et al., 2018; Oehen et al., 2013).

The acute effects of MDMA include a marked influence on the human endocrine system. Plasma concentrations of the hormones cortisol, dehydroepiandrosterone, prolactin and oxytocin are all increased in a dose-dependent manner following MDMA administration to human volunteers (Dumont et al., 2009; Harris et al., 2002; Hysek et al., 2013; Parrott, 2016). In addition, MDMA increased corticosterone, 11-dehydroxycorticosterone and aldosterone, where the latter two were significantly correlated with peak increases in

Rudnick and Wall, 1992; Simmler et al., 2013). Besides modulating synaptic monoamine concentrations, MDMA also displays affinity as an agonist at serotonin 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C}, α_{2A} adrenergic, dopamine D_1 and D_2 (Ball and Rebec, 2005; Eshleman et al., 2013; Rickli et al., 2015; Simmler et al., 2013), as well as adrenergic α_1 and β, muscarinic M_1 and M_2, histamine H_1 (Battaglia et al., 1988) and acetylcholine nicotinic receptors (Garcia-Ratés et al., 2010). While MDMA has some agonist properties at the human trace amine-associated receptor 1 (TAAR1), which has been associated with the

et al., 1998). Mild confusion as well as drunkenness and feeling stimulated and 'high' (Camí et al., 2000, Kolbrich et al., 2008) are also among the effects commonly observed after MDMA administration. It further produced a marked increase in feelings of mouth dryness, hot and cold sensations, alterations in sound and colour perception, tenseness, decreased appetite, dizziness, difficulty to concentrate, feelings of love for others, liking human company and feeling at peace with the world (Dumont et al., 2009; Harris et al., 2002). The last three emotional states are more typical of entactogenic effects, which seem to have a pronounced social and empathy-enhancing component (Greer and Tolbert 1986; Hysek et al., 2013; Kirkpatrick and de Wit, 2015), as well as increasing the perceived pleasantness of affective touch (Bershad et al., 2019). Perhaps most relevant for its

properties with the psychostimulants amphetamine, methamphetamine and methylphenidate, it also produces several subjective effects that are not observed in these drugs (Bershad et al., 2016; Dolder et al., 2018a; Kamilar-Britt and Bedi, 2015; Simmler and Liechti, 2018).

The importance of 5-HT for a compound's ability to produce entactogenic effects has been shown in receptor antagonism studies in human volunteers, where the subjective effects of MDMA were attenuated by the selective serotonin re-uptake inhibitors (SSRIs) citalopram, paroxetine and fluoxetine (Farré et al., 2007; Liechti and Vollenweider, 2000a; Tancer and Johanson, 2007). While the 5-HT_2 receptor antagonist ketanserin did not have

could indicate that changes in centrally available oxytocin may not have been fully captured in their study. Due to this relative lack of knowledge of how, and if, hormones contribute significantly to the therapeutic and subjective effects of MDMA, the endocrine-regulating effects of alternative entactogens were not considered as criteria for inclusion of these compounds in this review.

For the purpose of this review, compounds were chosen whose pharmacology is consistent with the above neurobiological effects, and whose safety profile is not inferior to that of MDMA. Firstly, compounds must not show indications of being more neurotoxic than MDMA. In the past, much of the resistance to studying MDMA in humans, with the

entactogens were identified by looking for specific themes and choices of words in the reports, which are indicative of MDMA-like effects. For instance, phrases like 'feeling talkative', 'had a long deep conversation', 'felt need to call friends', 'listened to a friend for a long time' etc., were used to identify prosocial and empathic effects. Similarly, phrases like 'in a good mood', 'feeling great', etc., or 'energised', 'awake', 'speedy', etc., were used to identify euphoric or stimulating effects. Similar analogous phrases were searched for to identify a compound's alleged ability to produce qualitative effects characterised by empathy, increased sociability, feeling at peace, openness, euphoria, stimulation and sedation among others. The same approach was also used to identify negative effects such as anxiety, malaise, confusion, lack of coordination/intoxication or hangovers.

effects.

Based on these criteria, the classic psychostimulants like amphetamine, methamphetamine or methylphenidate were excluded, even though they share some of the subjective sequalae of MDMA (Bershad et al., 2016; Oberlender and Nichols, 1988), because they do not potently increase synaptic availability of 5-HT (Liechti, 2015; Rothman et al., 2001; Simmler et al., 2013). While an argument can be made that compounds like 4-bromo-2,5-dimethoxyphenethylamine (2C-B) or N,N-diisopropyl-5-methoxytryptamine (5-MeO-DiPT) are also entactogenic, and they have been described as

ring substituted with an alkylamine side chain at the β position. MDMA itself belongs to this class, and the unique effects of its members such as 1-(1,3-benzodioxol-5-yl)-*N*-methyl-2-butanamine (MBDB) (Figure 1d) are what first prompted researchers to postulate the category of entactogens as a distinct pharmacological class (Nichols, 1986; Nichols et al., 1986; Ratcliffe, 1974). The most-studied 1,3-bezodioxole besides MDMA is its N-desmethyl lower homologue, 3,4-methylenedioxyamphetamine (MDA) (Figure 1c), which has a long history of recreational and psychotherapeutic use that even predates that of MDMA (Climko et al., 1987; Kurland et al., 1976; Naranjo et al., 1967; Stolaroff, 2004; Yensen, 1975; Yensen et al., 1976). MDA is therefore unique among the compounds on

serotonergic markers, but with lower potency than MDMA at behaviourally equivalent doses (Johnson and Nichols, 1989). The situation is somewhat different with MDEA which, while causing similar short-term depletion of 5-HT in rat synaptosomes, did not produce any measurable reduction in SERT binding 1 week post treatment with a single dose of 20 mg/kg (Schmidt, 1987). In a subsequent investigation, Colado et al. (1999a) found that, whereas a 15 mg/kg dose also did not produce a decrease in SERT binding sites, doses of 25–35 mg/kg did decrease SERT binding sites, about half as severely as 15 mg/kg MDMA. The same study also found a slight decrease in 5-HIAA in MDEA-treated rats. This is in agreement with Barrionuevo et al., (2000), who found that a dose of 40

but its affinity for binding to α_{2A} and 5-HT_{1A} receptors is approximately 10-fold that of MDMA (Rickli et al., 2015). In addition, MDA's R-enantiomer has about four-fold higher affinity as an agonist at 5-HT_2 receptors than its S-enantiomer (Lyon et al., 1986).

Like MDMA, the felt effects of MDA include euphoria, empathy, relaxation and feeling at peace with the world (Naranjo et al., 1967). It also increases introspection, self-awareness and acceptance (Climko et al., 1987; Turek et al., 1974). Consistent with its comparatively high affinity as an agonist at 5-HT_2 receptors (Rickli et al., 2015; Simmler et al., 2013), MDA also frequently produces alterations in vision, such as closed eye visions (Baggott et

interesting to note that several subjects were able to go to sleep during the study by Hermle et al. (1993), implying that MDEA has far lower stimulant qualities than MDMA. MDEA also displays a strong discrepancy in felt and neurological effects when its two enantiomers are studied separately. Spitzer et al. (2001) found that the S-isomer of MDEA produced typical entactogenic effects like increased talkativeness, openness and increased mood, while the R-isomer produced dysphoria and depressive symptoms. This, together with their neuroimaging results, led the authors to hypothesise that (R)-MDEA is largely responsible for neurotoxic effects, while (S)-MDEA is responsible for the entactogenic effects observed with the racemate. Users of MDEA generally confirm these

non-β-keto counterparts (Kelly, 2011; Valente et al., 2014). Nevertheless, there exists a limited number of substituted cathinones that show great promise as MDMA-like tools for psychotherapy. These are primarily 2-methylamino-(3,4-methylenedioxy)propiophenone (methylone) (Figure 2d), and, to a lesser extent, 2-ethylamino-(3,4-methylenedioxy)propiophenone (ethylone) (Figure 2e) and 2-methylamino-(3,4-methylenedioxy)butyrophenone (butylone) (Figure 2f), which are similar in action to methylone, albeit less potent (Majchrzak et al. 2018).

concentration of cathinone (Valente et al., 2014). Any cathinone containing a primary amine in its side chain can rapidly dimerise after its formation, leading to an inactive product. This would certainly apply to MDCATH, which would make it unsuitable for clandestine distribution and could explain the absence of user reports.

Nevertheless, the limited research that exists on MDCATH has shown that, in drug discrimination trials, MDCATH substituted for MDMA, but failed to substitute for the psychedelic amphetamine DOM or the classic psychostimulant dextroamphetamine (Figure 2a) (Dal Cason et al., 1997), indicating that any pharmacological effects it

suggesting that, despite its high selectivity for catecholamines, it may nevertheless retain some MDMA-like qualities.

The aminoethyl and butyrophenone homologues of methylone – ethylone and butylone – also show some promise as potential MDMA substitutes, but to this day there exists only a limited amount of research concerning their toxicity, pharmacodynamics and qualitative effects. The studies that are available have shown that these two compounds do exhibit some methylone-like effects (López-Arnau et al., 2012; Supplementary file: Erowid 'Ethylone', 2006a, (1,2,3,7,8); Erowid 'Butylone', 2005a, (1,7,8,9,10) and users report their

would fall well within the range employed by Baumann et al. (2012).

The effects of methylone on monoamine levels and transport have been studied *in vitro* (Cozzi et al., 1999; Eshleman et al., 2013; López-Arnau et al., 2012; Nagai et al., 2007; Simmler et al., 2013) as well as in live rats (Baumann et al., 2012; López-Arnau et al., 2014). Methylone displays an approximately equal ability to cross the blood–brain barrier as MDMA (Simmler et al., 2013).

While the neurochemical effects of methylone clearly resemble those of MDMA in several respects, there is evidence to suggest that methylone nevertheless exerts its action via

[^{3}H]NE with a potency similar to that of MDMA, but inducing the release of [^{3}H]5-HT with somewhat lower potency than MDMA. The same ability to release [^{3}H]monomamine neurotransmitters was also observed via the transporters hDAT, hSERT and hNET expressed in human embryonic kidney cells (HEK 293) (Eshleman et al., 2013), indicating that methylone's ability to release [^{3}H]monoamines is not restricted to rodents, and that human neurochemistry is likely similarly affected by it. The same authors found that butylone was not a potent releaser of neurotransmitters, except for 5-HT, which implies that its stimulant effects are likely induced by transport inhibition rather than direct release of monoamines from vesicles. Finally, ethylone actually proved to be more potent

Users report that the effects of methylone are very similar to those of MDMA overall, but are different in some subtle ways (Supplementary file: Erowid 'Methylone', 2001, (5,6,7,8,9)). Overall, methylone is shorter acting than MDMA, lasting about half as long, with a peak of about 2 h followed by another 2–3 h of reduced after-effects (Table 2). At a dose of around 125 mg, most users experience the effects as being somewhat milder than MDMA, with less euphoria, but with greater clarity of thought and ability to communicate (Supplementary file: Erowid 'Methylone', 2001, (1,2,4,6,7,10,12)). Furthermore, methylone and the other two cathinones discussed, all produce feelings of

APB', 2011, (1); Erowid '5-MAPB', 2014, (3)); Reddit '6-APB', 2018). Interestingly, users report that using SSRIs in combination with 6-APB does not reduce its felt effects (Supplementary file: Erowid '6-APB', 2011, (12,14,17)). In contrast, it has been shown that SSRIs can greatly diminish the felt entactogenic effects of MDMA (Farré et al., 2007; Liechti and Vollenweider, 2000a; Tancer and Johanson, 2007). Users report having self-administered 6-APB during 3 consecutive days without having to increase the dosage, although longer periods of consumption did produce a tolerance to the material (Supplementary file: Erowid '6-APB', 2011, (9,11)). On the other hand, under similar

2014, (1,2,7); Erowid '6-APB', 2011, (1,2,3,4,6,7,8,10,12); Erowid '6-MAPB', 2014, (1); Reddit '5-MAPB', 2014). Despite their sympathomimetic action, users generally report a feeling of profound clear-minded calmness similar to MDMA. The typical doses are around 60–100 mg for the *meta*-benzofurans (6-APB and 6-MAPB) and around 50–80 mg for the *para*-benzofurans (5-APB and 5-MAPB) (Supplementary file: Erowid '5-APB', 2011; Erowid '5-MAPB', 2014; Erowid '6-APB', 2011; Erowid '6-MAPB', 2014) (Table 2). At these doses, 6-MAPB is slightly more stimulating than MDMA, while 6-APB and 5-MAPB are more entactogenic. Furthermore, 6-MAPB and 6-APB are also reported to have mild psychedelic effects at high doses, while 5-APB and 5-MAPB are reported as being more purely

users (Baumann and Rothman, 2009).

Aminoindanes

Aminoindanes are included in this report because they seem to possess many of the qualitative effects of MDMA, but also seem to completely lack the serotonergic neurotoxicity of MDMA (Gallagher et al., 2012; Sainsbury et al., 2011). A consistent structural commonality among all of the compounds examined so far, as well as the ones discussed in later sections, is that they possess a non-constrained alkyl-chain attached to

given to human test subjects, either clinically or clandestinely, which means that one cannot yet say with certainty that its effects are MDMA-like in humans.

Furthermore, N-methylation of psychoactive phenethylamines tends to decrease their psychedelic effects while increasing their psychostimulant and entactogenic effects (Nichols, 1986; Shulgin and Shulgin, 1991). For instance, MDA and MDMA, and amphetamine and N-methylamphetamine, obey this structure–activity relationship. It therefore stands to reason that the aminoindanes obey the same structure–activity relationship, and that the N-methyl homologues of MDAI and 5-IAI, 5,6-methylenedioxy-2-(methylamino)indane (MDMAI) and 5-iodo-2-(methylamino)indane (5-IMAI), respectively,

potent [^{3}H]5-HT uptake inhibitors as well as non-vesicular [^{3}H]5-HT releasers (Halberstadt et al., 2019; Johnson et al., 1991c). 5-IAI was about twice as potent at inhibiting the uptake of [^{3}H]5-HT into synaptosomes than MDAI, which, in turn, was slightly less potent than MDMA at producing this effect (Table 1). These tests also showed that 5-IAI was about half as potent at inhibiting [^{3}H]DA uptake, and inducing non-vesicular [^{3}H]DA release, as MDMA. MDAI, on the other hand, did not produce any strong effects on [^{3}H]DA. 5-IAI inhibited [^{3}H]NE uptake at about two-thirds, and MDAI at less than one-third of the potency of MDMA. Furthermore, both compounds displayed high selectivity in their action

and a perceived increase in body temperature also seem to be a common effect. Furthermore, users also report that despite the increased ease with which they are able to communicate while under the influence of these two compounds, they only report very mild euphoria when compared with MDMA (Drugs Forum '5-IAI', 2010, Supplementary file: Erowid 'MDAI', (2010), (2,3,4)). The qualitative effects reported by users do seem to differ from the *in vitro* results when it comes to noradrenergic action, however. While both MDAI and 5-IAI resulted in efflux, as well as inhibition of uptake of NE from and into human cell cultures (Simmler et al., 2014), users generally reported the effects of both aminoindanes to be less stimulating than MDMA. Users do not complain about insomnia following

aminobutyl)indole (Bulatova and Suvorov, 1968) (Figure 5a), is a substituted tryptamine that was in use as an antidepressant drug under the trade name 'Monase' in the 1950s (Jacob and Upjohn Co, 1967; Murphree et al., 1961) before being withdrawn from the market due to concerns that regular α-ET use could lead to agranulocytosis (Butin, 1962). This means that, along with MDA, α-ET is relatively unique among all the pharmacological substances evaluated here, in that a body of medical data exists about it, and its use in humans has been well documented (Bylenga, 1961; Kiessling, 1961; Murphree et al., 1961; Perlstein, 1961; Settel, 1961; Shulgin and Shulgin, 1997).