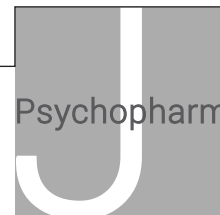# Beyond ecstasy: Alternative entactogens to 3,4-methylenedioxymethamphetamine with potential applications in psychotherapy

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Abstract

The last two decades have seen a revival of interest in the entactogen 3,4-methylenedioxy-N-methylamphetamine (MDMA) as an adjunct to psychotherapy, particularly for the treatment of post-traumatic stress disorder. While clinical results are highly promising, and MDMA is expected to be approved as a treatment in the near future, it is currently the only compound in its class of action that is being actively investigated as a medicine. This lack of alternatives to MDMA may prove detrimental to patients who do not respond well to the particular mechanism of action of MDMA or whose treatment calls for a modification of MDMA's effects. For instance, patients with existing cardiovascular conditions or with a prolonged history of stimulant drug use may not fit into the current model of MDMA-assisted psychotherapy, and could benefit from alternative drugs. This 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

Introduction

Since it was first synthesised under the name *methylsafrylamin* by the pharmaceutical company Merck in 1912 (Bernschneider-Reif et al., 2006), the entactogen 3,4-methylenedioxy-N-methyl-amphetamine (MDMA) (Figure 1b) has had a turbulent history filled with controversy and conflicting views about its place in society. After decades of relative obscurity, MDMA resurfaced in the 1970s (Greer, 1983; Shulgin and Nichols, 1978) and was adopted by many underground therapists who used its unique effects in their work with patients (Greer, 1985; Greer and Tolbert, 1985, 1990; Passie, 2018). Due to its euphoric and pro-social, empathy-enhancing qualities, MDMA soon escaped this small enclave of medical practitioners and gained widespread popularity in the dance-club scene and later in the rave scene (McDowell and Kleber, 1994; Reynolds, 2013; Schwartz and Miller, 1997). Alarmed by its growing popularity, as well as by some sensationalised incidences of overdoses, lawmakers around the world quickly moved to ban MDMA and place it in the most restrictive category of their drug laws, where it has remained ever since (Nutt, 2008; US Food and Drug Administration, 2017). For almost two decades, scientific research on the effects of MDMA had been severely hampered by its legal status, limiting our understanding of any potential therapeutic applications that it may have.

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 Torre et al., 2004; Jerome et al.,

2013; Parrott, 2007; Patel and Titheradge, 2015; Sessa et al., 2019). At the forefront of this new wave of research is the Multidisciplinary Association for Psychedelic Studies (MAPS), who conducted an early trial with MDMA in humans and published the results in 2011 (Mithoefer et al., 2011), which opened new avenues of research. Since then, MAPS and other scientific institutions have conducted a host of clinical trials to ascertain MDMA's effectiveness in treating post-traumatic stress disorder (PTSD) (Mithoefer et al., 2018; Oehen et al., 2013; Ot'alora et al., 2018). The outcomes of these trials have yielded highly favourable results, which suggest that MDMA-assisted psychotherapy is significantly more effective at treating PTSD than any other treatment currently available. This led the United States Food and Drug Administration (FDA) to grant breakthrough therapy status to MDMA in 2017 (MAPS, 2019), thereby agreeing to expedite and aid the approval process if it stands up to further scrutiny. MDMA is currently in Phase 3 clinical trials and is expected to appear on the market as a treatment for PTSD in 2021 (Mithoefer et al., 2019).

MDMA is relatively unique in that it is currently the only substance in its class of action that is being actively studied for its efficacy as an aid in psychotherapy. MDMA is perhaps the most famous example among a class of psychoactive drugs called

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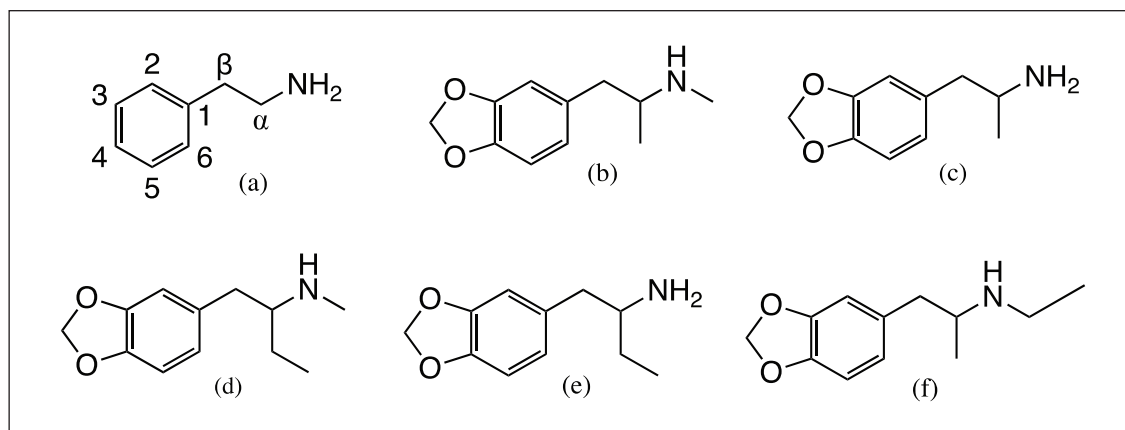
Figure 1. (a) Phenethylamine, (b) MDMA, (c) MDA, (d) MBDB, (e) BDB, (f) MDEA.
BDB: 1-(1,3-benzodioxol-5-yl)-2-butanamine; MBDB: 1-(1,3-benzodioxol-5-yl)-*N*-methyl-2-butanamine; MDA: 3,4-methylenedioxyamphetamine; MDEA: 3,4-methylene-dioxy-N-ethyl-amphetamine; MDMA: 3,4-methylenedioxy-N-methylamphetamine.

entactogens (latin: touching within (Nichols, 1986)) or sometimes *empathogens*. Since no other drug in this class of action is currently being studied as a treatment for PTSD and psychotherapy in general, this means that, within the foreseeable future, psychiatry is limited to using MDMA when entactogenic effects are required in the course of a patient's treatment. This lack of alternative medicines in treatments involving MDMA could prove to be detrimental to patients who do not respond well to the specific mechanisms of action of MDMA, or whose psychiatric condition calls for a slightly modulated, albeit similar, range of effects. For instance, elderly patients or patients with existing heart conditions may not be able to tolerate the cardiovascular effects of MDMA, which has led to their exclusion from past clinical trials with this substance. Patients who have a long history of MDMA use may not 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 necessary to find alternative compounds that share the entactogenic qualitative effects of MDMA, which make it so useful in psychotherapy, while also possessing a safety profile that is equal or superior to that of MDMA.

Review of the pharmacology and subjective effects of MDMA

The pharmacological effects of MDMA share several features with classic psychostimulants, such as amphetamine, as well as classic psychedelics such as lysergic acid diethylamide (LSD). In addition, MDMA produces some distinct effects unlike those of psychostimulants or psychedelics, which set it apart from these pharmacological classes and might be deemed 'entactogen effects' (Bershad et al., 2016; Dumont and Verkes, 2006; Holze et al., 2020; Shulging and Nichols, 1978). The known pharmacology of MDMA will briefly be summarised here for the purpose of comparing and contrasting the known pharmacology of alternative MDMA-like compounds with that of MDMA.

In humans, the acute physiological effects of MDMA include mydriasis, jaw clenching and bruxism, insomnia, anorexia and nystagmus (Farré et al., 2004; Green et al., 2003; Holze et al., 2020; Mas et al., 1999). In a clinical setting, MDMA did not cause hyperthermia when administered to volunteers at doses of around 1.5 mg/kg (Mas et al., 1999; Vollenweider et al., 1998), but was found to increase core body temperature by 0.3–0.6°C in a subsequent investigation at a dose of 2 mg/kg (Freedman et al., 2005). For a review of the thermal effects of MDMA in humans, see Parrott (2012). For clinical purposes, the cardiovascular effects of MDMA are the major safety concern. MDMA consistently induces an increase in heart rate as well as in systolic and diastolic blood pressure (Downing, 1986; Grob et al., 1996; Hysek et al., 2012b; Kirkpatrick and de Wit, 2015; Lester et al., 2000). Some volunteers developed transient hypertensive symptoms after receiving a therapeutic dose of MDMA (Vizeli and Liechti, 2017; Vollenweider et al., 1998), which, while not leading to any medical complications, has led to concerns about the potential 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 systolic blood pressure (Seibert et al., 2014). Additionally, MDMA, or one of its metabolites, increases copeptine and vasopressin (Dolder et al., 2018a; Forsling et al., 2001; Simmler et al., 2011).

MDMA's effects on neurotransmission are well studied in both rodents and humans (Table 1), where it has been shown to be a potent agent for inhibiting membranal monoamine transporters and for releasing the monoamines serotonin (5-HT), norepinephrine (NE) and dopamine (DA) into the synaptic cleft from presynaptic neurons (Eshleman et al., 2017; Gough et al., 1991; Liechti, 2015; Nichols, 1986; Simmler et al., 2013; Verrico et al., 2007; Zsilla et al., 2018). In humans, the relative selectivity for monoamine modulation is NE > 5-HT > DA. During monoamine uptake into the neuronal cytoplasm, Na^+, Cl^- and one molecule of the neurotransmitter are transported via the membranal transporter protein in a single step, followed by a second step in which K^+ is transported out of the neuron via the transporter protein (Rudnick and Clark, 1993). Artificially increasing the extracellular K^+ concentration can reverse this transport process by transporting Na^+, Cl^- and neurotransmitter out of the cell, while transporting K^+ into the cell. MDMA can take the place of K^+ in this process by acting as a substrate that is transported into the neuron in exchange for Na^+, Cl^- and neurotransmitter (Rudnick and Wall, 1992). MDMA thus directly stimulates efflux of cytoplasmic monoamines by reversing the action of biogenic monoamine transporters. In addition, MDMA also acts as a substrate for the vesicular monoamine transporter $VMAT_2$, which sequesters monoamines into vesicles for later release into the synaptic cleft during exocytosis (Henry et al., 1994). It causes efflux of monoamines from vesicles into the cytoplasm by inhibiting the transport of monoamines into the vesicle via the $VMAT_2$ and by dissipating the pH gradient across the vesicular membrane, which helps drive uptake of monoamines into the vesicles (Partilla et al., 2006; Rudnick and Clark, 1993). In addition, MDMA also binds to monoamine transporters and to $VMAT_2$ and inhibits their function directly (Battaglia et al., 1988; Partilla et al., 2006; Rudnick and Wall, 1992; Simmler et al., 2013). Besides modulating synaptic monoamine concentrations, MDMA also displays affinity as an agonist at serotonin $5\text{-}HT_{1A}$, $5\text{-}HT_{2A}$, $5\text{-}HT_{2B}$ and $5\text{-}HT_{2C}$, 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 regulation of monoamine transporters and dopaminergic activity (Miller, 2011), its activity is significantly lower at human TAAR1 than at rodent TAAR1 (Simmler et al., 2016).

In humans and rats, MDMA use produces a reduction in serotonergic markers, characterised by a decrease in serotonin transporter (SERT) binding sites (Cowan, 2017; Kish et al., 2010; McCann et al., 2008; Schmidt et al., 1987) as well as a decrease in 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of 5-HT, in human cerebrospinal fluid (McCann et al., 2000), but not in the plasma (Stuerenburg et al., 2002). Additionally, postsynaptic $5\text{-}HT_2$ receptor sites are increased (Di Iorio et al., 2012; Urban et al., 2012). Meta-analyses by Mueller et al. (2016) and Müller et al. (2019) found that these alterations in serotonin binding sites achieved significance in heavy MDMA users (>50 lifetime usage) (Müller et al., 2019), but that these results were not conclusive in studies examining moderate users (Mueller et al., 2016). While the exact mechanisms underlying these neurotoxic effects remain poorly understood, it is known that in rats they

depend on both DA and 5-HT modulation (Costa et al., 2017; Colado et al., 1999a; Granado et al., 2008; Hewitt and Green 1994; Schmidt et al., 1985), as well as autophagy (Mercer et al., 2017; Shih et al., 2019). At high doses, MDMA can also cause the degeneration of 5-HT nerve terminals. This process is believed to be mediated through a combination of oxidative stress, metabolic compromise and inflammation (Yamamoto and Raudensky, 2008).

The subjective effects of acute MDMA exposure include enhanced mood and wellbeing and moderate derealisation, depersonalisation, thought disorder and anxiety (Vollenweider 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 therapeutic potential, it was found that while MDMA increased self-report anxiety, it decreases social anxiety, increased sociability, openness and authenticity (Baggott et al., 2016; Dolder et al., 2018a; Kamboj et al., 2018; Wagner et al., 2017). These results are consistent with previous findings that MDMA decreases the perceived intensity of social rejection (Bedi et al., 2010; Frye et al., 2014). These clinical findings are also corroborated by field research where recreational MDMA users were asked to relate their experiences (Baylen and Rosenberg 2006; Carlyle et al., 2019). Another effect of MDMA seems to be to increase cognitive and emotional empathy, while decreasing sensitivity to negative emotional stimuli and the ability to recognise negative emotions in others (Carhart-Harris et al., 2014; Doss et al., 2018; Frye et al., 2014; Hysek et al., 2012a; Kuypers et al., 2017, 2018a).

Essential entactogenic pharmacology of MDMA, and exclusion criteria for alternative compounds

While all of the pharmacological properties of MDMA likely contribute to its unique effects, there seem to be some that are essential to its entactogenic and therapeutic qualities, while others may not be as essential and some – such as the potential to cause hypertensive episodes – are even undesirable.

One of the key neuropharmacological properties of MDMA that distinguishes it, and other entactogens, from the classic psychostimulants like amphetamine, is its pronounced ability to increase the synaptic availability of 5-HT in addition to the catecholamines DA and NE (Liechti and Vollenweider, 2001; Nichols 1986). For the purpose of this review, a compound will be considered a psychostimulant if it has the ability to potently increase catecholamines but not 5-HT, while an entactogen must show an appreciable ability to additionally modulate 5-HT. These differences in the neurochemical

Table 1. In vitro monoamine release and re-uptake data. All values are in µM. Re-uptake data is the IC50 value for uptake inhibition, unless otherwise specified. The number in brackets represents the reference from which the data is taken (see bottom of table). Release data is the EC50 value.

Compound	Transporter inhibition			Monoamine release		
	SERT	DAT	NET	5-HT	DA	NE
MDMA	1.36 ± 0.64 (1)*	17 ± 7 (1)*	0.447 ± 0.154 (1)*	5.63 ± 3.57 (1)*	22 ± 31 (1)*	NA (1)*
	1.340 ± 0.280 (2)*	1.020 ± 0.291 (2)*	0.375 ± 0.060 (2)*	0.874 ± 0.035 (2)*	1.290 ± 0.198 (2)*	0.267 ± 0.025 (2)*
	0.425 ± 0.041 (3)**	1.442 ± 0.120 (3)**	0.405 ± 0.040 (3)**			
	0.238 ± 0.013 (4)**	1.572 ± 0.059 (4)**	0.462 ± 0.018 (4)**			
				1.9 ± 0.4 (5)**	>30 (5)**	4.5 ± 4.2 (5)**
	0.382 ± 0.053 (6)*	0.410 ± 0.045 (6)*	0.108 ± 0.015 (6)*	1.10 ± 0.29 (6)*	7.5 ± 2.3 (6)*	0.360 ± 0.092 (6)*
				1.04 ± 0.27 (7)*	4.8 ± 2.3 (7*)	0.57 ± 0.19 (7)*
	34.8 ± 1.1 (8)*	NA (8)*	6.6 ± 1.1 (8)*			
	0.72 ± 0.19 (9)**	1.4 ± 0.32 µM (9)**	0.66 ± 0.21 (9)**	0.058 ± 0.015 (9)**	0.20 ± 0.046 (9)**	0.086 ± 0.023 (9)**
	0.125 ± 0.011 (10)**	1.009 ± 0.039 (10)**	0.450 ± 0.030 (10)**	0.039 ± 0.005 (10)**	0.042 ± 0.002 (10)**	0.053 ± 0.007 (10)**
MDA	0.478 ± 0.040 (3)*	0.890 ± 0.100 (3)*	0.266 ± 0.028 (3)*			
	4.9 ± 1.9 (11)*	20.5 ± 0.2 (11)*	0.42 ± 0.18 (11)*	Known releaser (11)*	Known releaser (11)*	Known releaser (11)*
MBDB	2.04 ± 0.96 (1)*	22 ± 4 (1)*	2.80 ± 1.30 (1)*	2.49 ± 4.41 (1)*	>100 (1)*	NA (1)*
	0.784 ± 0.052 (3)**	7.825 ± 0.888 (3)**	1.233 ± 0.123 (3)**			
	1.8 ± 0.48 (9)**	6.3 ± 1.4 (9)**	2.7 ± 0.75 (9)**	0.54 ± 0.16 (9)**	No Effect (9)**	3.3 ± 0.87 (9)**
MDEA	72.2 ± 1.1 (8)*	NA (8)*	49.7 ± 1.2 (8)*			
	1.27 ± 0.43 (1)*	9.3 ± 1.7 (1)*	1.02 ± 0.28 (1)*	2.88 ± 2.12 (1)*	>100 (1)*	NA (1)*
				0.4 (12)**	6.91 (12)**	Unknown (12)**
Methylone	0.23 ± 0.03 (13)**	0.56 ± 0.05 (13)**	0.53 ± 0.05 (13)**			
	5.75 ± 0.68 (14)*	0.819 ± 0.168 (14)*	1.22 ± 0.13 (14)*			
	1.92 ± 0.35 (7)*	0.343 ± 0.024 (7)*	0.234 ± 0.055 (7)*	6.7 ± 2.78 (7)*	11.8 ± 5.6 (7)*	0.426 ± 0.067 (7)*
	15.5 ± 10.5 (1)*	4.82 ± 1.28 (1)*	0.542 ± 0.208 (1)*	>10 (1)*	>100 (1)*	NA (1)*
	1.017 ± 0.059 (10)**	1.232 ± 0.133 (10)**	1.031 ± 0.162 (10)**	0.234 ± 0.035 (10)**	0.117 ± 0.012 (10)**	0.140 ± 0.017 (10)**
	2.3 ± 0.58 (9)**	2.9 ± 0.67 (9)**	0.74 ± 0.24 (9)**	0.22 ± 0.068 (9)**	0.22 ± 0.068 (9)**	0.093 ± 0.026 (9)**
	63.3 ± 6.4 (15)*	4.21 ± 0.3 (15)*	13.9 ± 1.3 (15)*			
Ethylone	4.46 ± 0.74 (1)*	5.68 ± 0.82 (1)*	2.54 ± 0.66 (1)*	9.90 ± 30.10 (1)*	>100 (1)*	NA (1)*
	0.464 ± 0.075 (6)*	1.72 ± 0.45 (6)*	1.42 ± 0.20 (6)*	1.48 ± 0.25 (6)*	>10 (6)*	>10 (6)*
Butylone	0.68 ± 0.13 (13)**	1.71 ± 0.32 (13)**	0.98 ± 0.13 (13)**			
	1.97 ± 0.43 (7)*	0.211 ± 0.054 (7)*	1.06 ± 0.24 (7)*	3.1 ± 1.4 (7)*	>10 (7)*	>100 (7)*
	6.22 ± 2.78 (1)*	2.90 ± 0.6 (1)*	2.02 ± 0.52 (1)*	5.5 ± 11.5 (1)*	>100 (1)*	NA (1)*
6-APB	2.698 (Ki) (16)*	0.150 (Ki) (16)*	0.117 (Ki) (16)*			
	0.93 ± 0.23 (11)*	3.3 ± 1.2 (11)*	0.19 ± 0.11 (11)*			
	0.290 ± 0.062 (17)*	0.121 ± 0.022 (17)*	0.020 ± 0.004 (17)*	0.85 ± 0.15 (17)*	0.582 ± 0.088 (17)*	0.051 ± 0.012 (17)*

(Continued)

Table 1. (Continued)

Compound	Transporter inhibition			Monoamine release		
	SERT	DAT	NET	5-HT	DA	NE
6-MAPB	0.3 (18)*	0.03 (18)*	0.04 (18)*			
	0.496 ± 0.074 (17)*	0.052 ± 0.017 (17)*	0.033 ± 0.002 (17)*	0.91 ± 0.24 (17)*	0.86 ± 0.12 (17)*	0.64 ± 0.21 (17)*
5-APB	0.811 (Ki) (16)*	0.265 (Ki) (16)*	0.180 (Ki) (16)*			
	0.29 ± 0.21 (11)*	6.1 ± 2.9 (11)*	0.16 ± 0.14 (11)*	Known releaser (11)*	NA (11)*	NA (11)*
5-MAPB	0.137 ± 0.024 (17)*	0.099 ± 0.010 (17)*	0.073 ± 0.018 (17)*	0.40 ± 0.14 (17)*	2.61 ± 0.68 (17)*	0.58 ± 0.21 (17)*
MDAI	0.512 ± 0.38 (19)**	5.920 ± 0.690 (19)**	1.426 ± 0.147 (19)**			
				0.114 ± 0.015 (20)**	1.334 ± 0.226 (20)**	0.117 ± 0.017 (20)**
	0.59 ± 0.13 (6)*	3.48 ± 0.46 (6)*	0.192 ± 0.036 (6)*	2.9 ± 1.2 (6)*	24 ± 11 (6)*	0.57 ± 0.20 (6)*
	8.3 ± 11.7 (21)*	31 ± 10 (21)*	0.65 ± 0.19 (21)*			
	0.212 (22)**	19.793 (22)**	11.618 (22)**			
5-IAI	0.241 ± 0.021 (19)*	0.992 ± 0.090 (19)*	0.612 ± 0.035 (19)*			
	0.879 (Ki) (16)*	1.590 (Ki) (16)*	0.311 (Ki) (16)*			
	2.5 ± 0.6 (21)*	23 ± 12 (21)*	0.76 ± 0.22 (21)*	Known releaser (21)*	Known releaser (21)*	Known releaser (21)*
α-ET	0.7 (23)**	NA (23)**	NA (23)**	3.8 (23)**	NA (23)**	NA (23)**
	0.6 ± 0.3 (24)**	15 ± 5 (24)**	3.2 ± 0.8 (24)**			
4-FA	2.352 ± 0.290 (22)**	0.270 ± 0.033 (22)**	0.356 ± 0.015 (22)**	0.0232 ±0.0017 (25)**	0.232 ± 0.017 (25)**	0.640 ± 0.076 (25)**
	6.8 ± 1.5 (9)**	0.77 ± 0.16 (9)**	0.42 ± 0.12 (9)**	0.73 ± 0.24 (9)**	0.20 ± 0.048 (9)**	0.037 ± 0.089 (9)**
	94.83 ± 9.2 (15)*	9.5 ± 0.1 (15)*	10.3 ± 0.3 (15)*			
	14 ± 3 (26)*	3.9 ± 1.3 (26)*	0.15 ± 0.6 (26)*			
	205 ± 25 (27)*	21 ± 10 (27)*	1.8 ± 0.3 (27)*			
	19 ± 14 (11)*	3.7 ± 2.0 (11)*	0.20 ± 0.08 (11)*			

1) Simmler et al. (2013); 2) Verrico et al. (2007); 3) Johnson et al. (1991c); 4) Rothman et al. (2001); 5) Fitzgerald and Reid (1993); 6) Eshleman et al. (2017); 7) Eshleman et al. (2013); 8) Montgomery et al. (2007); 9) Nagai et al. (2007); 10) Baumann et al. (2012); 11) Rickli et al. (2015); 12) O'Loinsigh et al. (2001); 13) López-Arnau et al. (2012); 14) Cozzi et al. (1999); 15) Rosenauer et al. (2012); 16) Iversen et al. (2013); 17) Eshleman et al. (2019); 18) Shimshoni et al. (2017); 19) Johnson et al. (1991c); 20) Halberstadt et al. (2019); 21) Simmler et al. (2014); 22) Marona-Lewicka et al. (1995); 23) Ask et al. (1989); 24) Rényi and Ross (1985); 25) Blough et al. (2014); 26) Luethi et al. (2019); 27) Zwartsen et al. (2017).

*Data from human cell cultures; **data from rat cell cultures.

5-APB: 5-(2-aminopropyl)-benzofuran; 6-APB: 6-(2-aminopropyl)-benzofuran; DA: dopamine; DAT: dopamine transporter; α-ET: α-ethyltryptamine; 4-FA: 4-fluoroamphetamine; 5-HT: serotonin; 5-IAI: 5-iodo-2-aminoindane; 6-MAPB: 5-(2-methylaminopropyl)benzofuran; 5-MAPB: 5-(2-methylaminopropyl)benzofuran; MBDB: 1-(1,3-benzodioxol-5-yl)-N-methyl-2-butanamine; MDA: 3,4-methylenedioxyamphetamine; MDAI: 5,6-methylenedioxy-2-aminoindane; MDEA: 3,4-methylenedioxy-N-ethyl-amphetamine; MDMA: 3,4-methylenedioxy-N-methylamphetamine; NA: not available; NE: norepinephrine; NET: norepinephrine transporter; SERT: serotonin transporter.

effects of MDMA and psychostimulants are also mirrored in their subjective effects. While MDMA shares many 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 significant effects on ratings of increased mood, it significantly reduced the perceptual changes produced by MDMA (Kuypers et al., 2018a; Liechti et al., 2000). However, the 5-HT$_{1A}$ receptor antagonist pindolol did not seem to significantly alter any of MDMA's subjective effects, with the exception of decreasing confusion, suggesting a minimal role of this receptor in mediating the felt effects of MDMA (Kuypers et al., 2014).

While increasing 5-HT availability seems to be essential for producing MDMA-like entactogenic effects, there is also evidence that 5-HT by itself may not sufficient. For instance, SSRIs do not seem to produce MDMA-like qualitative effects (Marona-Lewicka and Nichols, 1998). Furthermore, pre-treatment with the dopamine D$_2$ receptor antagonist haloperidol reduced the enhancement of mood, and increased feelings of malaise and anxiety (Liechti and Vollenweider, 2000b), while the norepinephrine transporter (NET) inhibitor reboxetine reduced the stimulant effects and the 'blissful state' and 'experience of unity' elicited by MDMA (Hysek et al., 2011). Interestingly, pre-treatment with the α$_1$- and β-adrenoreceptor antagonists carvedilol did not modify the subjective effects of MDMA, but significantly decreased its adverse cardiovascular effects (Hysek et al., 2012b).

The contribution of the endocrine effects of MDMA to its entactogenic properties are generally not well studied yet. The exception to this is the effect of oxytocin, which was found to contribute to the socioemotional effects of MDMA in an early study (Dumont et al., 2009). In contrast, a later study failed to reproduce these results on prosocial feelings, and did not find any significant correlation between oxytocin and the socioemotional effects of MDMA (Kuypers et al., 2014). It should be noted that both studies measured oxytocin levels only in the plasma, which makes the results somewhat difficult to interpret. In a separate study, intranasal administration of oxytocin did increase both plasma and cerebrospinal fluid concentrations of oxytocin, but the levels in these two fluids were poorly correlated (Striepens et al., 2013. As was mentioned by Kuypers et al. (2014), this 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 aim of developing it into a medicine, has stemmed from concerns that it may have intolerable long-term neurotoxic effects (Parrott, 2014). While it is now clear that many of the earlier concerns of human neurotoxicity were exaggerated and that administering therapeutic doses of MDMA in a clinical environment probably does not cause long-term adverse effects to patients (Halpern et al., 2004; Ludewig et al., 2003; Müller et al., 2019; Thal and Lommen, 2018), the neurotoxic potential of other MDMA-like drugs nevertheless remains an important concern and must be evaluated carefully in each case. This is a very important requirement, as this is a key factor for determining the safety of patients and whether a compound can be expected to be approved for medical use by regulatory authorities. Consequently, compounds which are less neurotoxic than MDMA were actively sought out. Additionally, MDMA-like entactogens that seem to produce less cardiovascular stress were also searched for. Compounds were also excluded if they did not possess *in vitro* pharmacology indicative of potent neuronal 5-HT modulation together with catecholamine modulation of at least one of the neurotransmitters DA or NE.

Finally, since this review examines all of these compounds for their potential applications in psychotherapy, where their subjective effects are key, their ability to produce states of lowered emotional defensiveness, characterised by increased openness, authenticity, empathy and self-acceptance together with mental lucidity, was also looked for. There is some evidence that the long-term therapeutic benefits of MDMA are mediated by an increase in the personality trait of openness (Wagner et al., 2017), and it is therefore reasonable to hypothesise that the aforementioned emotional states also play a role, although further research is needed to confirm this. When possible, these socioemotional effects were confirmed in the evaluated substances by analysing reports of volunteers who had received various doses of these compounds in clinical settings. Since such studies were lacking for many compounds, however, the online reports of users who had consumed these substances clandestinely were analysed in those cases instead (see the supplementary file for detailed references and stored copies of user reports). MDMA-like 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.

These criteria are largely informal, and are intended as general summaries of reported effects to give the reader a phenomenological understanding of the felt experience produced by these drugs, rather than as a rigorous classification of a compound's qualitative sequalae. While such a rigorous classification would of course be desirable, it would have been very difficult to execute in

this case, due to the relatively small number of available reports for some of these compounds and the high variability in the choice of words and report styles employed by users. Positive identification of a substance, as well as verification of the dose consumed, is also impossible from such reports, but sampling several reports nevertheless allowed a picture of some common features of a given substance's subjective effects to emerge. Contamination of reports due to poly-drug use was controlled for by only considering reports where a single substance had been reported to be used. The final requirement for an entactogen to be considered for this list was therefore that its qualitative effects feel substantially similar to those of MDMA.

In summary, potential alternatives were excluded if they met one or more of the following exclusion criteria:

(a) Negligible potency for neuronal 5-HT modulation;
(b) Negligible potency for both neuronal DA and NE modulation;
(c) High potency for 5-HT$_{2A}$ receptor agonism (i.e. predominantly psychedelic effects (Nichols, 2016));
(d) Neurotoxic effects exceeding those of MDMA;
(e) Serious acute health risks not present in MDMA;
(f) Major deviations from the _in vitro_ pharmacology of MDMA;
(g) Insufficient information to (at least anecdotally) confirm qualitative MDMA-like 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 such in the past (González et al., 2015; Palamar and Acosta, 2020; Schifano et al., 2019), they were also excluded due to their high affinity as agonists at post-synaptic 5-HT$_2$ and 5-HT$_{1A}$ receptors (Fantegrossi et al., 2006; Nugteren-van Lonkhuyzen et al., 2015; Taylor et al., 1986; Villalobos et al., 2004), which would indicate that their effects also include a marked psychedelic component. While it is certainly possible that these two compounds, and others like them, may be useful for psychotherapy, their effects are – strictly speaking – not MDMA-like, for which reason they were excluded from this review.

This review covers compounds from the chemical classes of the 1,3-benzodioxoles, cathinones, benzofurans and aminoindanes as well as some atypical entactogens from the indole class and simple amphetamine derivatives. The following data were reviewed for each included compound:

1. Studies evaluating the ability of compounds to substitute for MDMA in rodents, in drug discrimination paradigms.
2. Research examining the neurotoxicity of the compounds in question.
3. The _in vitro_ pharmacology and, in particular, the action of compounds at plasmalemmal monoamine transporters,

postsynaptic 5-HT receptors and other relevant neurobiological targets.
4. Clinical studies and subjective effects.

1,3-benzodioxoles

The 1,3-benzodioxoles are the class of amphetamine derivatives containing a methylenedioxy moiety attached to the benzene ring at the 3 and 4 positions when numbered with respect to the alkylamine side-chain – or equivalently, a 1,3-benzodioxole ring substituted with an alkylamine side-chain at the 5 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 this list in that there exists a body of clinical work directly investigating its efficacy as an adjunct to psychotherapy.

The 1,3-benzodioxoles examined in this section are MDA, MBDB and N-ethyl-3,4- methylenedioxyamphetamine (MDEA, often abbreviated as MDE in the earlier literature) (Figure 1f) (Freudenmann and Spitzer, 2004), the N-ethyl homologue of MDMA. Another potentially useful 1,3-benzodiole is the α-ethyl homologue of MDA, 1-(1,3-benzodioxol-5-yl)-2-butanamine (BDB) (Figure 1e). The _in vitro_ pharmacological profile of BDB seems to be similar to that of MDMA for modulating monoamine levels, but with lower potency (Johnson et al., 1986; Nagai et al., 2007). BDB substituted for MDMA in rats trained to discriminate MDMA from saline (Nichols et al., 1986) and had similar, albeit more sedating, effects to MDMA in humans (Shulgin and Shulgin, 1991), suggesting that it may be a therapeutically useful alternative to MDMA too. Unfortunately, apart from these promising-looking results, BDB suffers from a general paucity of research and consequently cannot be fully reviewed as a potential replacement for MDMA here.

MDA, MBDB and MDEA all fully substituted for MDMA in drug discrimination studies in rats (Glennon and Misenheimer, 1989; Oberlender and Nichols, 1988; Rangisetty et al., 2001). Additionally, the stimulus produced by 2,5-dimethoxy-4-methyl-amphetamine (DOM), LSD and mescaline generalised to (R)-MDA but not to (S)-MDA, and the stimulus of the psychostimulants cocaine and dextroamphetamine generalised to (S)-MDA but not to (R)-MDA (Baker and Taylor, 1997; Glennon and Young, 1984a, 1984c). Interestingly, neither enantiomers of MBDB or MDEA substituted for dextroamphetamine or DOM (Glennon et al., 1989; Nichols and Oberlender, 1989), which would be consistent with a more 'pure' entactogen stimulus.

Repeated MDA administration has been shown to cause a reduction of SERT and 5-HIAA similar to that seen with MDMA in the rat brain (Battaglia et al., 1987, Colado et al., 1995; Ricaurte et al., 1985; Stone et al., 1986). MBDB also causes a reduction in the same 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 mg/kg MDEA, but not 20 mg/kg MDEA, produced a 20–30 % decrease in SERT binding sites. Overall, this suggests that both MBDB and MDEA are less neurotoxic than MDMA, with MDEA possessing about one quarter of the neurotoxic potential of MDMA (Colado et al., 1999a; Ricaurte et al., 1987).

The pharmacodynamic effects of the 1,3-benzodioxoles are similar to those of MDMA, although all compounds also exhibit some marked differences, which are reflected in their qualitative and pharmacological effects. MDA releases neuronal 5-HT from rat brain tissue with approximately equal potency as MDMA, but releases DA with slightly higher potency than its N-methyl homologue (Johnson et al., 1986; McKenna et al., 1991; Wichems et al., 1995). On the other hand, MDA released 5-HT slightly more potently, and DA and NE about equipotently, than MDMA in HEK 293 cells (Rickli et al., 2015). Surprisingly, *in vitro* data concerning the effects of MDA on monoamines is somewhat sparse, but the data that exists indicates that the potency of MDA to inhibit uptake of neurotransmitters into cell cultures is lowest for the dopamine transporter (DAT) and displays the following relative potency for inhibition of monoamine transporters NET > SERT > DAT (Table 1). MBDB and MDEA possess similar neuropharmacological profiles to MDMA, but are significantly less selective for inducing the release and inhibiting the re-uptake of DA compared with 5-HT (Freudenmann and Spitzer, 2004; Van Aerts et al., 2000). The relative potency for monoamine modulation by MBDB is 5-HT > NE >> DA (Table 1). In fact, the two separate studies failed to determine MBDB's potency for releasing DA (Nagai et al., 2007; Simmler et al., 2013), suggesting that MBDB does not truly function as a DA-releasing agent.

MDEA showed the same relative selectivity for increasing extracellular levels of monoamines of 5-HT > NE >> DA, but, to our knowledge, its ability to release neuronal NE has not yet been investigated. MBDB and MDEA also possess a similar binding affinity at 5-HT$_{1A}$ and α_{2A} receptors as MDMA, but only MDEA exhibits a similar potency for binding to 5-HT$_{2A}$ receptors as MDMA (Simmler et al., 2013). MDA also binds to these receptors, 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 al., 2010). MDA therefore shares most of the effects of MDMA, but additionally has a mild psychedelic component that is not seen to the same degree with MDMA (Baggott et al., 2019). Recreational users of MDA also confirm these effects, and report that MDA shares most of MDMA's qualitative features. As with MDMA, users report emotional effects ranging from euphoria, empathy, authenticity, a desire to communicate with others and relate personal issues, to increased introspection and clarity of thought. Again, the major difference with MDMA reported by most users is that MDA is said to be slightly less stimulating, and has a greater tendency to produce alteration in visual perception, such as brightened colours, closed eye visions, and, more rarely, mild hallucinations (Supplementary file: Erowid 'MDA', 2000, (1—15)). While the dosage of MDA to achieve full entactogenic effects seems to be very similar to MDMA, its acute effects generally last around 2 h longer (Table 2). High-dose, or repeated use, frequently leads to unpleasant after-effects, and can produce a 'come down' similar to that experienced by some recreational users of MDMA.

MDEA has been given to volunteers in a clinical setting (Gouzoulis et al., 1993a), and several studies have directly assessed its subjective effects in humans (Hermle et al., 1993; Spitzer et al., 2001). MDEA was found to have anxiolytic properties, increase feelings of openness and interest in interpersonal relationships, and increased participant's interest in questions pertaining to their life (Hermle et al., 1993). In the same study, one subject became anxious and developed hallucinations (Gouzoulis et al., 1993b), although it should be pointed out that this result is somewhat difficult to interpret since the subject fell asleep and developed these symptoms upon being awakened. It is 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 effects, and report that it produces effects that are very similar to those of MDMA, but less euphoric and clear-minded, and with a sedating component (Supplementary file: Erowid 'MDE', 2000, (1—4); Shulgin and Shulgin, 1991).

While large-scale formal clinical trials with MBDB in humans have not yet been conducted, it has been administered to humans in a manner where the dose and identity of the substance was confirmed (Nichols et al., 1986; Shulgin and Shulgin, 1991). These trials revealed that MBDB lacks any psychedelic effects, but also lacks the stimulant effects that are present in MDMA. Its effects were described as facilitating introspection, emotional openness and communication. (S)-MBDB was found to be the more active and more entactogenic enantiomer. These reports are in agreement with other anecdotal accounts, which state that the effects of MBDB are very similar to those of MDEA, albeit not quite as sedating (Supplementary file: Erowid 'MBDB', 2001, (2, 3, 5, 6, 7, 8)). Whereas an improvement in mood is generally

Table 2. Typical oral dose and duration of reviewed compounds. Number in brackets refers to the reference for dose/duration (see bottom of table).

Compound	Dose (mg)	Duration of acute effects (hours)
MDMA	100–150, (1)	3–6, (1)
MDA	80–130, (2)	5–8, (2)
MBDB	180–210, (3)	4–6, (3)
MDEA	100–200, (3, 4, 5)	3–5, (3, 4, 5)
Methylone	100–250, (6)	2–3.5, (6)
Ethylone	150–250, (7)*	2–4, (7)*
Butylone	150–250, (8)*	2–5, (8)*
6-APB	80–100, (9)	6–9, (9)
6-MAPB	50–100, (10)*	6–8, (10)*
5-APB	60–80, (9)	3–8, (9)
5-MAPB	30–70, (11)	5–6, (11)
MDAI	100–175, (12)	2–5, (12)
5-IAI	100–200, (13)*	2–4, (13)*
α-ET	100–150, (14)	6–8, (14)
4-FA	50–120, (15, 16)	3–7, (15, 16)

1) MAPS (2019); **2)** Baggott et al. (2019); **3)** Shulgin and Shulgin (1991); **4)** Ensslin et al. (1996); **5)** Brunnenberg et al. (1998); **6)** Kelly (2011); **7)** Erowid 'Ethylone' (2006a); **8)** Erowid 'Butylone' (2005a); **9)** Roque Bravo et al. (2019); **10)** Drugs Forum '6-MAPB' (2011); **11)** Erowid '5-MAPB' (2014); **12)** Erowid 'MDAI' (2010); **13)** Drugs Forum '5-IAI' (2010); **14)** Shulgin and Shulgin (1997); **15)** Dolder et al. (2018a); **16)** de Sousa Fernandes Perna et al. (2018). *Dose estimated from anecdotal user reports.
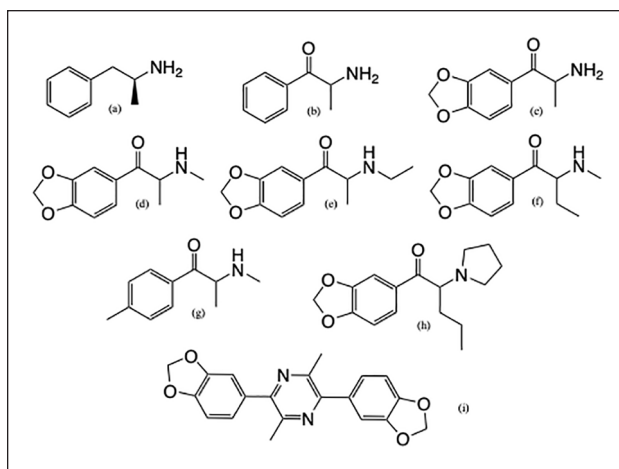5-APB: 5-(2-aminopropyl)-benzofuran; 6-APB: 6-(2-aminopropyl)-benzofuran; α-ET: α-ethyltryptamine; 4-FA: 4-fluoroamphetamine; 5-IAI: 5-iodo-2-aminoindane; 6-MAPB: 5-(2-methylaminopropyl)benzofuran; MDA: 3,4-methylenedioxyamphetamine; MDMA: 3,4-methylenedioxy-N-methylamphetamine; MBDB: 1-(1,3-benzodioxol-5-yl)-*N*-methyl-2-butanamine; MDAI: 5,6-methylenedioxy-2-aminoindane; MDEA: 3,4-methylenedioxy-N-ethyl-amphetamine.

Figure 2. (a) Dextroamphetamine, (b) cathinone, (c) MDCATH, (d) methylone, (e) ethylone, (f), butylone, (g) mephedrone, (h) MDPV, (i) MDCATH dimer.
MDCATH: 2-amino-(3,4-methylenedioxy)propiophenone; MDPV: methylenedioxypyrovalerone.

reported, it seems to lack the pronounced euphoric component of MDMA (Supplementary file: Erowid 'MBDB', 2001, (1,3,4,8,10)). Like MDMA, MBDB also produces a strong desire to socialise and relate one's emotions to others, and seems to be only moderately less effective for this purpose than MDMA, in that it is alleged to not afford users the same degree of mental clarity (Supplementary file: Erowid 'MBDB', 2001,(1,4,7,10)).

Cathinones

Cathinones or β-keto amphetamines are the class of substituted amphetamines containing a carbonyl group at the β position of the phenethylamine skeleton (Figure 1a). This makes them structurally similar to adrenaline and noradrenaline (NA), which both possess a hydroxy group at the β position of their phenethylamine skeleton.

Overall, it seems that cathinones tend to favour psychostimulant, amphetamine-like effects over entactogenic, MDMA-like effects, albeit often at a lower potency than their 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).

Methylone is just the β-keto analogue of MDMA, which raises the obvious question of whether 2-amino-(3,4-methylenedioxy)propiophenone (MDCATH) (Figure 2c) would also possess a useful pharmacological profile due to its being the β-keto analogue of MDA. Surprisingly, very little scientific data exists for this compound and, perhaps even more surprisingly, there is no mention of it in anecdotal user reports, suggesting that it has not appeared as a recreational drug on the black market in any serious capacity. The fact that MDCATH has never been exploited as a street drug may be due to its propensity for forming biologically inactive dimers (Figure 2i). Cathinone itself is known to rapidly dimerise after it is prepared or biosynthesised in plants, which is why users of khat (*catha edulis*) value fresh khat leaves over dried ones since they contain a significantly higher 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 possesses are purely entactogenic as opposed to psychedelic or psychostimulating. These results could indicate that if MDCATH is stabilised in a manner that prevents the formation of dimers, it may in fact be one of the most entactogenic and MDMA- or MDA-like cathinones of all. However, it is difficult to draw firm conclusions about the therapeutic and socioemotional effects in humans from such discrimination studies. Clinical research is therefore necessary to determine if MDCATH is indeed entactogenic. MDCATH was also shown to inhibit monoamine transporters, albeit with less

selectivity for SERT and with somewhat lower potency than MDA (Rickli et al., 2015). Further research on its effects and on its chemical stability is clearly warranted.

Two cathinones that are not considered here but that may seem like potential candidates are 4,N-dimethylcathinone (mephedrone) (Figure 2g) and methylenedioxypyrovalerone (MDPV) (Figure 2f). Mephedrone is reported by some users to possess effects that can be subjectively similar, albeit somewhat more stimulating, to those of MDMA (Winstock et al., 2011). It is also the most studied of all the substituted cathinones (Papaseit et al., 2016). Studies in rat neuronal tissue preparations have shown that mephedrone favours dopamine re-uptake inhibition compared with the same effects on serotonin (Hadlock et al., 2011; Martínez-Clemente et al., 2012), which indicates that its effects differ from those of MDMA and may be less entactogenic. Furthermore, mephedrone has been shown to elicit substantially more pronounced compulsive behaviour in rats than MDMA (Aarde et al., 2013; Hadlock et al., 2011) and is generally believed to have greater abuse potential than the latter (Brunt et al., 2011; Winstock et al., 2011). Overall, these properties indicate that mephedrone may not be an ideal substitute for MDMA in clinical applications.

MDPV may seem like a potential MDMA-like drug due to its methylenedioxy moiety, but *in vitro* studies have shown that it almost completely lacks effects on 5-HT, compared with its effects on catecholamines, and that its pharmacological profile is more closely related to that of methamphetamine than to that of MDMA. It did, however, substitute for both of these compounds in drug discrimination studies using rats (Fantegrossi et al., 2013), 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 effects to be somewhat MDMA-like, although ethylone is reported to be less stimulating (Reddit 'Ethylone', 2015), while butylone is reported to be similar to, or slightly more stimulating than methylone (Drugs Forum 'Butylone', 2010). As this data is anecdotal, it cannot replace drug discrimination or clinical trials, but it does provide some indications that these two compounds may possess qualitative properties that could make them useful substitutes for MDMA in therapeutic applications, and that they should be investigated further to evaluate their medical potential.

Finally, methylone, the cathinone whose chemical structure most closely resembles that of MDMA, unsurprisingly also seems to possess the greatest pharmacological similarities to MDMA, albeit with some intriguing differences. Methylone was shown to lack dopamine neurotoxic effects in mice (Anneken et al., 2015; Granado et al., 2008), but exacerbated these neurotoxic effects when co-administered together with MDMA. An in vivo study in adolescent rats found that high-dose repeated administration of methylone produced serotonergic impairment and memory deficits in rats but had little effect on mice (Den Hollander et al., 2013). Adverse effects on 5-HT systems seem to be strongly

dose-dependent however: Baumann et al. (2012) found that rats treated with three consecutive doses of 3–10 mg/kg exhibited no long-term changes in brain monoamine levels, whereas López-Arnau et al. (2014) and Den Hollander et al. (2013) showed that two consecutive doses of 10–30 mg/kg for 4 consecutive days (*binge dosing*) produced persistent brain 5-HT depletion even 2 weeks after administration of the final dose in rats (Baumann et al., 2012; Den Hollander et al., 2013; López-Arnau et al., 2014). Den Hollander et al. (2013) further showed that, despite their high-dose binge regimen of 4 × 30 mg/kg, the rats that had been treated with methylone did not perform worse than saline-treated rats in tests designed to assess memory and cognition.

Taken together, these results indicate that methylone likely does not produce any lasting negative effects on monoamine systems and cognition when administered in therapeutic applications, as the frequency of administration and the doses used in such contexts 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 somewhat different mechanisms than the former drug. López-Arnau et al. (2014) found that pretreatment with *para*-chlorophenylalanine (pCPA), a 5-HT synthesis inhibitor, fully inhibited the increased locomotor activity observed in rats after administration of MDMA, but did not have any effect on the increased motor activity observed after administration of methylone (López-Arnau et al., 2012).

Methylone was also shown to be a potent monoamine re-uptake inhibitor (Cozzi et al., 1999; López-Arnau et al., 2012; Nagai et al., 2007; Simmler et al., 2013) and, specifically, an inhibitor of SERT, DAT and NET (Table 1). For these transporters, methylone seems to inhibit DAT and NET at approximately half the potency of MDMA, while inhibiting SERT at about one-third of the potency of MDMA. However, unlike MDMA, methylone does not appear to be a very potent inhibitor of the vesicular monoamine transporter 2 (VMAT2), a property it seems to share with other β-keto amphetamine analogues (Cozzi et al., 1999; López-Arnau et al., 2012). These authors further found that butylone exhibited similar inhibitory effects, albeit with approximately three-fold lower potency than methylone, except for its inhibition of NET, which was inhibited only half as potently as by methylone (Table 1). The study by Simmler et al. (2013) found that ethylone too was a potent inhibitor of SERT, DAT and NET in a manner similar to that of butylone, with the major difference being that it caused less inhibition of DA uptake (Table 1).

Overall, these cathinones all exhibit similar re-uptake inhibitory effects on neuronal membrane transporters as MDMA, but with slightly lower selectivity for SERT, and overall lower potency. The most striking difference in their action is their comparably very low potency at inhibiting the vesicular monoamine transporter VMAT2, suggesting once again that, despite their similar subjective effects, the entactogenic cathinones manifest these qualities via slightly different pharmacodynamic mechanisms than MDMA.

Additionally, methylone proved to be a potent monoamine releaser in rat brain synaptosomes (Nagai et al., 2007), inducing the release of tritium-labelled [3H]DA and [3H]NE with a potency similar to that of MDMA, but inducing the release of [3H]5-HT with somewhat lower potency than MDMA. The same ability to release [3H]monoamine 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 [3H]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 at releasing 5-HT than methylone, but did not cause the release of DA from preloaded neurons (Simmler et al., 2013), indicating that its effects are more serotonergic than those of other cathinones.

Methylone and butylone displayed some affinity for binding to 5-HT$_{2A}$ receptors although at significantly lower potencies than MDMA (Eshleman et al., 2013). The same authors also found that both methylone and butylone are partial agonists at the 5-HT$_{1A}$ receptor and, in addition, had weak antagonist effects on 5-HT$_{2C}$ receptors, which is markedly different from MDMA, with the latter being a partial agonist rather than an antagonist. In a separate study, neither methylone, ethylone or butylone displayed affinity for binding to 5-HT$_{1A}$, 5-HT$_{2A}$ or 5-HT$_{2C}$ receptors, with the only exception being that ethylone displayed an affinity as an agonist at 5-HT$_{1A}$ receptors similar to that of MDMA (Simmler et al., 2013).

Overall, these results show that the entactogenic cathinones examined in this section all have effects on monoamine neurotransmitters that are similar to those of MDMA, but are about half as potent at manifesting their effects as MDMA. The cathinones also display a slight selectivity for modulating catecholamines over 5-HT compared with MDMA, but this bias does not seem pronounced enough to subjectively attenuate their entactogenic effects as is the case with MDPV. The overall drop in potency of these three cathinones, compared with the potency of MDMA, is consistent with the doses reported by recreational users of these compounds (Table 2). Some pharmacodynamic differences did, however, become apparent. Most notably, the cathinones did not inhibit the vesicular transporter VMAT2, displaying a clear selectivity toward inhibition of membrane transporters instead. Taken together with the fact that users report the subjective effects of these compounds to be very similar to those of MDMA, these results imply that inhibition of VMAT2 does not seem to be a prerequisite for inducing MDMA-like, entactogenic effects in humans.

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 inner peace and mental calmness much like those
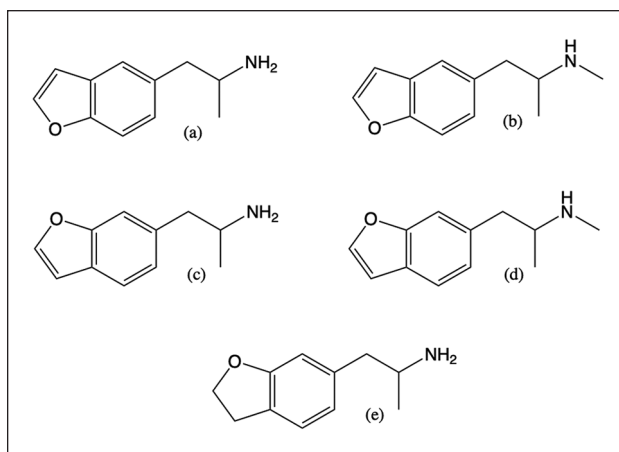
Figure 3. (a) 5-APB, (b) 5-MAPB, (c) 6-APB, (d) 6-MAPB, (e) 6-APDB. 6-APB: 6-(2-aminopropyl)-benzofuran; 5-APB: 5-(2-aminopropyl)-benzofuran; 6-APDB: 2,3-dihydro isomer of 6-APB 5-MAPB; 6-MAPB: 5-(2-methylaminopropyl) benzofuran.

produced by MDMA (Supplementary file: Erowid 'Methylone', 2001, (1,2,4,5)). Methylone is also reported to produce an increased desire to socialise, though not to the extent that MDMA does (Supplementary file: Erowid 'Methylone', 2001, (1,2,3,5,7,12)). At these doses, users also do not complain about significant negative alterations in mood, such as depression or lethargy, after the acute effects have worn off. Doses at or above about 200 mg produce an effect that many users describe as being difficult to distinguish from MDMA in its qualitative effects. At doses above 250 mg, negative effects such as tachycardia, hangover and insomnia increase relative to the desirable effects (Supplementary file: Erowid 'Butylone', 2005b, (3,4,6,11); Erowid. 'Ethylone', (5), 2006b; Erowid 'Methylone', 2001, (5,8,11)).

Benzofurans

The benzofurans discussed in this paper are a class of compounds that can be thought of as amphetamines containing a furan moiety on the benzene ring. They share close structural similarities with MDMA and MDA, but are distinguished from these compounds by containing one less oxygen atom. This generates an additional degree of freedom in choosing whether to have the oxygen atom *para* or *meta* to the alkylamine side chain of the benzene ring. 5-(2-aminopropyl)-benzofuran (5-APB) (Figure 3a) and 5-(2-methylaminopropyl)benzofuran (5-MAPB) (Figure 3b) are the *para* benzofuran analogues of MDA and MDMA, while 6-(2-aminopropyl)-benzofuran (6-APB) (Figure 3c) and 6-(2-methylaminopropyl)benzofuran (6-MAPB) (Figure 3d) are the *meta* benzofuran analogues. Also of interest are the 2,3-dihydro isomers of these compounds, where the aromaticity of the benzofuran ring is broken by the addition of two hydrogen atoms across the π -bond in the furan ring. The 2,3-dihydro versions of the entactogenic benzofurans were first synthesised in an attempt to determine which oxygen atom in MDMA and MDA is more important for their neuropharmacology (Monte et al., 1993).

The benzofurans listed above exhibit some intriguing pharmacological and qualitative effects that make them potential

substitutes for MDMA. One of the few drug-discrimination studies performed in rats using benzofurans found that 5-APB, as well as 6-APDB (the 2,3-dihydro isomer of 6-APB) (Figure 3e), fully substituted for MDMA in rats trained to discriminate MDMA from vehicle (Dolan et al., 2017).

To date, no research has been conducted to ascertain the neurotoxic potential of benzofurans (Roque Bravo et al., 2019). There are, however, some indications coming from user reports: 5-APB and 6-APB are generally claimed to produce less of a 'come down', a period following the acute effects of a drug, characterised by depressed thoughts, lack of energy and general malaise, than MDMA (Supplementary file: Erowid '5-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 circumstances, MDMA already produced significant tolerance by the third day (Shulgin and Shulgin, 1991).

This may be especially important for therapists wishing to use an entactogen as an adjunct to psychotherapy over the course of many sessions as opposed to the two or three drug-assisted sessions that are typically employed with MDMA (Mithoefer, 2015). While these reports can provide some useful clues, it must be emphasised that they all come from anecdotal statements. The benzofurans should therefore be treated with the assumption that they have at least the same neurotoxic potential as MDMA. More research is clearly needed here to definitively ascertain the toxicity of these compounds.

In vitro studies have shown that 6-APB, 5-MAPB and 6-MAPB are all inhibitors of the rat DAT, NET and SERT (Monte et al., 1993; Shimshoni et al., 2017) and 6-APB, 5-MAPB and 6-MAPB are inhibitors of the human monoamine transporters hDAT, hNET and hSERT (Eshleman et al., 2019; Iversen et al., 2013). Most benzofurans inhibited monoamine transporters with the following relative potencies: NET > SERT > DAT, although some studies found 5-APB and 6-APB to be more selective for inhibiting DAT (Table 1). 5-MAPB, 6-MAPB, 5-APB and 6-APB have also been shown to be potent monoamine releasing agents (Table 1) (Eshleman et al., 2019; Rickli et al., 2015). In addition, *in vivo* studies found that 5-MAPB greatly increased extracellular concentrations of DA, NE and 5-HT, and that 5-MAPB was significantly more potent at eliciting this response than MDMA (Fuwa et al., 2016). Furthermore, all four benzofurans discussed here were also agonists at the 5-HT$_{1A}$, 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors (Rickli et al., 2015; Shimshoni et al., 2017).

These data indicate that the above discussed benzofurans all possess pharmacological profiles similar to that of MDMA. This is further corroborated by most user reports, where the subjective effects of the benzofurans are often likened to those of MDMA, and are reported to produce the same feelings of openness, inner peace and ability for non-judgmental reflection (Supplementary file: Erowid '5-APB', 2011, (1,2); Erowid '5-MAPB', 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-APB', 2014; Erowid '6-APB', 2011; Erowid '6-APB', 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 entactogenic (Supplementary file: Erowid 6-APB, 2011, (4,5,6,9,11,12); Erowid 6-MAPB, 2014, (1)). As with most MDMA-like entactogens, negative side effects worsen as the dose is increased, and users report more problems (Supplementary file: Erowid '5-APB', 2011, (3,5); Erowid '5-MAPB', 2014, (4); Erowid '6-APB', 2011, (1,3,15,16)).

The fact that users report the effects of 6-APB as having a slightly more psychedelic character than MDMA, particularly at higher doses, is not entirely surprising, since structurally it is an analogue of MDA, whose R-enantiomer has been shown to produce more psychedelic effects than its S-enantiomer (Glennon and Young, 1984a, 1984b, 1984c; Nichols et al., 1986).

Some users actually claim to prefer the effects of 6-APB because of the increased empathy, lower degree of stimulation and increased duration of effects produced by this compound compared with MDMA. (Reddit '6-APB', 2016). 5-APB and 6-APB are consistently reported to induce MDMA-like effects (Erowid '5-APB' 2011, Erowid '6-APB' 2011), albeit with some noteworthy differences: The onset of effects is generally described as more gradual and less 'forced' than the onset of MDMA. The duration of the entactogenic effects is also described as being longer (around 5–8 h for all four of the benzofurans as opposed to 3–6 h for MDMA) (Table 2) with greater mental clarity than MDMA. This could prove to be useful in a therapeutic setting to facilitate clear communication between the patient and the therapist, while lowering the possibility of having the session terminated prematurely as a result of the shorter duration of MDMA.

Finally, in addition to their more tolerable post-effect profile, some benzofurans may also prove to be less cardiotoxic than their MDMA and MDA counterparts. Shimshoni et al. (2017) found that 6-MAPB displayed significantly lower agonist affinity at the 5-HT$_{2B}$ receptor compared with MDMA. The authors of the study point out that this could indicate that 6-MAPB has a significantly lower risk of potentiating valvular heart disease, as the 5-HT$_{2B}$ receptor agonist properties of MDMA have been linked to such conditions in its 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
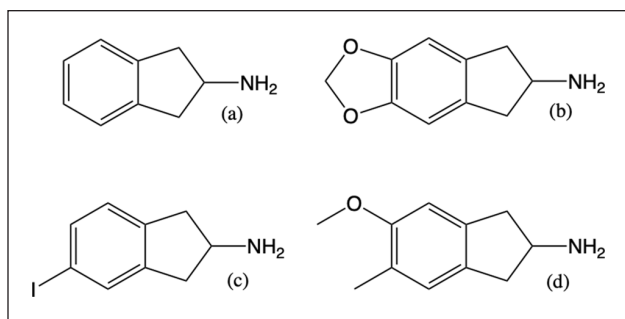
Figure 4. (a) 2-AI, (b) MDAI, (c) 5-IAI, (d) MMAI.
2-AI: 2-aminoindane; 5-IAI: 5-iodo-2-aminoindane; MDAI: 5,6-methylenedioxy-2-aminoindane; MMAI: 5-methoxy-6-methyl-2-aminoindane.

the α-carbon of the phenethylamine skeleton (Figure 1a and Figure 2b) (amphetamine tail). The aminoindanes differ from these other compounds in that their α-methyl group is also attached to the benzene ring, thus forming a propylene bridge. This creates a structure that is inherently bicyclic and thus lacks some of the rotational freedom that the other compounds here enjoy (Figure 4a) (Brandt et al., 2013).

Two specific aminoindanes will be examined: 5,6-methylenedioxy-2-aminoindane (MDAI) (Figure 4b) and 5-iodo-2-aminoindane (5-IAI) (Figure 4c). The reason for this is that these are the two most studied MDMA-like aminoindanes, and whereas other compounds in this chemical class may well prove to be valuable tools themselves, there is simply not enough research and user data to confirm that they do indeed have the desired properties. Specifically, 5-methoxy-6-methyl-2-aminoindane (MMAI) (Figure 4d) substituted for MDMA in a drug discrimination paradigm using rats (Johnson et al., 1991b; Monte et al., 1993; Nichols et al., 1991). An *in vitro* study showed that MMAI was a highly selective 5-HT releasing agent (Halberstadt et al., 2019). However, to our knowledge, it has never been 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, may well exhibit a similar pattern. In fact, MDMAI fully substitutes for (+)-N-methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine [(+)-MBDB)] (Figure 1d), with an even greater potency than MDAI (Oberlender and Nichols, 1990). This supports the hypothesis that the N-methyl homologues of MDMA-like aminoindanes possess similar entactogenic effects as their parent compounds, since MDMA also fully substituted for (+)-MBDB in the same study.

Both MDAI and 5-IAI completely substituted for MDMA in drug discrimination paradigms in rats (Nichols et al., 1990, 1991), implying that they both exhibit entactogenic, MDMA-like subjective effects in rodents. The same authors also studied the

serotonergic neurotoxicity of both these substances and found it to be negligible when compared with MDMA. Neurotoxicity was measured by treating rats with a single acute dose of 40 mg/kg of either substance before sacrificing the animals 1 week later and measuring the levels of 5-HT and 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of 5-HT, as well as the number of SERT sites. The studies found that, at these same doses, the non-cyclically constrained analogues of MDAI and 5-IAI, MDA and 4-iodoamphetamine (PIA), respectively, both produced a significant reduction in all of these markers. MDAI, on the other hand, did not produce any reduction in serotonergic markers, and 5-IAI produced only a 15% or less reduction in the same markers, compared with that produced by PIA. While this indicates that 5-IAI may cause some neurotoxicity at these doses, it should be noted that the dose of 40 mg/kg used in the experiment is extremely high and is often lethal for many other monoamine modulating drugs (Barceloux, 2012). Furthermore, regular high-dose administration of 5-IAI has been linked to some cognitive deficits, such as lowered performance in various tasks designed to asses memory, in rats (Compton et al., 2018). However, at their dosing regimen of 20 mg/kg every 2 days during adolescence, the same study found no significant difference in cortical and subcortical 5-HT and DA levels between those rats that had received the 5-IAI and those that had not. To our knowledge, no similar study exists for MDAI.

In vitro studies in rat synaptosomal preparations have found that MDAI and 5-IAI are both potent [³H]5-HT uptake inhibitors as well as non-vesicular [³H]5-HT releasers (Halberstadt et al., 2019; Johnson et al., 1991c). 5-IAI was about twice as potent at inhibiting the uptake of [³H]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 [³H]DA uptake, and inducing non-vesicular [³H]DA release, as MDMA. MDAI, on the other hand, did not produce any strong effects on [³H]DA. 5-IAI inhibited [³H]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 on SERT and NET in comparison with DAT. This suggests that 5-IAI in particular, has similar pharmacodynamic properties as MDMA.

While the above-mentioned results come from studies in non-human tissue, similar effects on monoamine transport inhibition were also observed in human embryonic kidney cells (Eshleman et al., 2017; Iversen et al., 2013; Simmler et al., 2014) (Table 1). MDAI and 5-IAI were significantly more potent at inhibiting hSERT compared with hDAT, as well as at inducing the release of both of these [³H]neurotransmitters (Simmler et al., 2014). One major difference with these studies compared with Johnson et al. (1991c) was the finding that the potency of MDAI and 5-IAI to inhibit hNET and to induce the release of [³H]NE was greater than their ability to do the same for [³H]5-HT and [³H]DA. However, users generally report that the aminoindanes are far less 'stimulating' than their amphetamine counterparts or than MDMA. Since all three groups in the above studies used human embryonic kidney cells, and since the relative affinities were different in rat synaptosomes, it stands to reason that the aminoindanes can have significantly different effects depending on which cells they act on. 5-IAI is also known to release monoamines from HEK 293 cells with the relative potency of 5-HT > DA > NE, while MDAI showed the relative potency of 5-HT > NE > DA (Simmler et al., 2014) (Table 1).

Unlike MDAI, 5-IAI also displayed high binding affinity at the 5-HT$_{1A}$, 5-HT$_{2A}$, 5-HT$_{2B}$ and 5-HT$_{2C}$ receptors (Halberstadt et al., 2019; Iversen et al., 2013; Simmler et al. 2014). Both drugs did, however, display affinity for binding to the adrenergic receptors α_{2A}, α_{2B} and α_{2C}.

The qualitative effects of 5-IAI agree with the above findings in that most users report both MDAI and 5-IAI to be highly entactogenic, with increased desire to socialise and increased ease to talk about one's thoughts and feelings (Bluelight '5-IAI', 2011, Supplementary file: Erowid 'MDAI', (2010), (1,2,7,8,10,11)). Enhanced tactile perception 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 ingestion of either aminoindane (Bluelight '5-IAI', 2011, Supplementary file: Erowid 'MDAI', (2010), (1,3,4,5,10,11)). Typical doses for the aminoindanes are about 100–200 mg, and their acute effects last between 2 and 5 h (Table 2). Doses above 300 mg begin showing some negative effects, with a mild hangover and occasional headaches. However, at lower doses, the negative after effects and emotional hangover, which users frequently complain about with MDMA, seem to be absent. (Supplementary file: Bluelight '5-IAI', 2011; Drugs Forum '5-IAI', 2010; Drugs Forum 'MDAI', 2009; Erowid 'MDAI', 2010, (1,6,7,9,10,12,13)).

As stated before, *in vitro* studies did, however, reveal a significant difference in the noradrenergic effects of both compounds when they were evaluated in rat synaptosomes compared with HEK 293 cells, which is an effect that is also observed with MDMA. This implies that the action of MDAI and 5-IAI can vary considerably across tissue-class, which means that their effects in the human brain may differ from the results mentioned above, which might account for the specifically entactogenic effects reported by human users rather than sympathomimetic effects. Reliance on user reports is also somewhat problematic in this case because the prevalence of reports is scant, and positively identifying a substance from an anecdotal report is not possible. The sparseness of reports is likely due to the fact that aminoindanes never gained widespread popularity as recreational drugs despite fears that this might happen (Sainsbury et al., 2011), most likely because they lack the euphoric component of more popular psychostimulants and entactogens.

Other potential substitutes

α-Ethyltryptamine

Unlike all the compounds examined so far, which have been phenethylamine derivatives, the following compound is a tryptamine: Etryptamine or α-ethyltryptamine (α-ET), 3-(2-aminobutyl)indole (Bulatova and Suvorov, 1968) (Figure
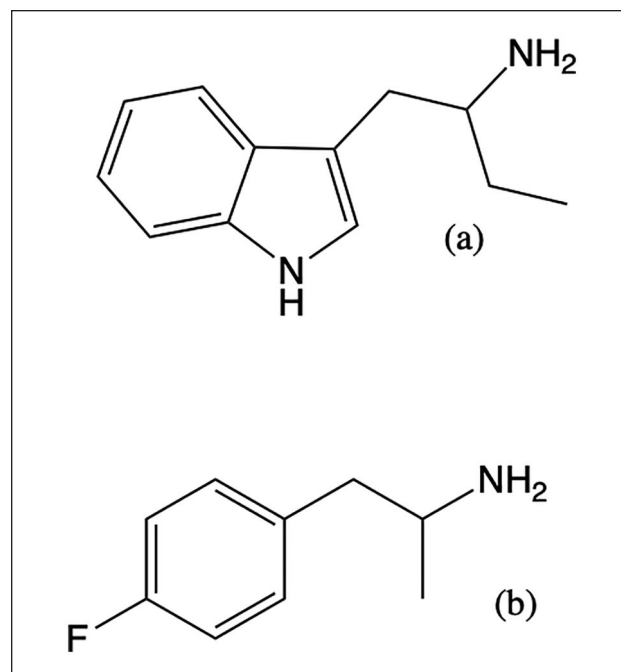
Figure 5. (a) α-ET, (b) 4-FA.
α-ET: α-ethyltryptamine; 4-FA: 4-fluoroamphetamine.

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).

α-ET fully substitutes for MDMA in MDMA-trained rats (Glennon, 1993; Glennon et al., 2006), supporting the notion that its qualitative effects are comparable with those of the latter. However, there seems to be some confusion in the literature about the distinct effects of the two enantiomers of α-ET. While earlier work found that DOM generalised to R-(–)-α-ET, but not to S-(+)-α-ET (Glennon et al., 1983), a later study found that the DOM stimulus generalised to (+)-α-ET but not to (–)-α-ET and that the dextroamphetamine stimulus generalised to (–)-α-ET but not to (+)-α-ET (Hong et al., 2001). If the latter finding is correct, it would mean that α-ET does not obey the structure–activity relationship of phenethylamines, that the R-enantiomer of an entactogenic phenethylamine usually has a more psychedelic character, whereas the S-enantiomer usually has a more psycho-stimulating character, as is the case with MDA for instance (Glennon and Young, 1984a, 1984b, 1984c; Nichols et al., 1986). This would be interesting in that it would indicate that this rule does not generalise to tryptamines. This pattern is also observed with other psychoactive phenethylamines (Shulgin and Shulgin, 1991), although one should bear in mind that α-ET is a tryptamine, not a phenethylamine and so perhaps the same reasoning does not apply to it. More research is needed to investigate this issue.

Despite the existing body of clinical research, the pharmacodynamic properties of α-ET have not been studied extensively in the laboratory. In terms of research on the potential neurotoxic properties of α-ET, the only existing data comes from a study where live rats were exposed to a binge-dosing regimen of 30 mg/kg of α-ET on eight consecutive occasions, spaced apart by 12 h (Huang et al., 1991). At 1 week following the last administration of a 30 mg/kg dose, the concentration of 5-HT and its metabolite 5-HIAA, as well as 5-HT uptake sites were measured in the test animals. The study also found a reduction in these markers, similar to that following administration of MDMA, indicating that -ET could have similar adverse effects on serotonergic neurons.

α-ET has been shown to be transported into serotonergic neurons via the SERT, and to elicit the release of [3H]5-HT (Ask et al., 1989) in rat brain slices. It has also been shown to have an inhibitory effect on the accumulation of [14C]5-HT, [3H]NE and [3H]DA in similarly prepared rat brain slices (Rényi and Ross, 1985), suggesting that α-ET can act as a neuronal monoamine uptake inhibitor. The potency to inhibit the accumulation of [14C]5-HT was, however, about 5- and 25-times greater than the potency to inhibit the accumulation of [3H]NE and [3H]DA, respectively. In rat brain synaptosomes, racemic α-ET proved to be a releaser of biogenic 5-HT, NE and DA, with about 10- and 28-times greater selectivity for 5-HT over DA and over NE, respectively (Blough et al., 2014) (Table 1). Again, the two optical isomers of α-ET displayed distinct profiles in their effects on monoamines: whereas both isomers were about equipotent in their ability to release 5-HT, the S-enantiomer was about 12- and 6-fold more potent at releasing DA and NE than the R-enantiomer (Table 1). Furthermore, while R-(–)-α-ET appeared to be inactive as a 5-HT$_{2A}$ receptor agonist, S-(+)-α-ET proved to be a partial agonist at this receptor, albeit with significantly lower potency than psychedelic tryptamines like α-methyltryptamine. These results partially explain why Hong et al. (2001) found that the DOM-like qualities of α-ET seem to reside in the S-enantiomer, but it is not clear how the R-enantiomer produces its dextroamphetamine-like effects since it is also the S-enantiomer that is more potent at increasing the levels of catecholamines. It also does not explain the earlier work by Glennon (1993), who found the opposite effects in the two enantiomers.

The qualitative effects of α-ET are described in detail by Shulgin and Shulgin (1997), and are consistent with what other users have reported. α-ET produces euphoric effects that are much more pronounced than with other psychoactive tryptamines and possesses entactogenic qualities much like MDMA (Supplementary file: Erowid 'AET', 2000, (1,2,4,5,6)). Despite being a partial 5-HT$_{2A}$ receptor agonist, it is generally not reported as having psychedelic effects, such as visual hallucinations (Supplementary file: Erowid 'AET', 2000, (2,3,4)). Consistent with the finding of Blough et al. (2014) that α-ET is selective for 5-HT and DA release over NE release, most users report that its stimulating effects are attenuated compared with those of MDMA. Some even report it as having sedative effects (Supplementary file: Erowid 'AET', 2000, (1,2,3,4,5)). This may make it particularly useful for patients for whom the stimulating effects of MDMA are too overwhelming, or who have existing heart conditions that may be exacerbated by sympathomimetic drugs.

At around 100 mg, most users report the effects of α-ET to be similar to MDMA, albeit less intense and longer lasting (Supplementary file: Erowid 'AET', 2000) (Table 2). It is described as producing euphoria, openness and empathy similar to MDMA but without causing stimulation. α-ET is said to be somewhat milder than MDMA with less of a 'rush' when the effects begin to manifest, and with less negative after-effects, which is further helped by the fact that it does not cause insomnia (Shulgin and Shulgin, 1997). At doses of around 100 mg, and even up to 200 mg, most users do not report experiencing a 'come down', although some do report mild lethargy immediately following the acute effects (Supplementary file: Erowid 'AET', 2000, (2,3,4,5)). Nevertheless, as with most entactogens, taking higher doses would be expected to produce more unwanted effects (Murphree et al., 1961; Shulgin and Shulgin, 1997; Supplementary file: Erowid AET, 2000, (2,6); Drugs Forum AET, 2006).

4-Fluoroamphetamine

Finally, the last compound examined in this report is the halogenated amphetamine *para*-fluoroamphetamine or 4-fluoroamphetamine (4-FA). All known *para*-halogenated amphetamines are psychoactive, but most have a rather worrisome safety profile, which makes them unsuitable for clinical applications. 4-Chloroamphetamine for instance, is a potent neurotoxin (Berger et al., 1989; Sanders-Bush and Steranka, 1978). 4-FA, on the other hand, possess a neurological safety profile that actually seems to be superior to that of MDMA, and possesses several other properties that make it a potential candidate for therapeutic applications.

To date, 4-FA has not been compared with MDMA in any drug discrimination paradigms in animals, although one study found that 4-FA substituted for dextroamphetamine in rats, but failed to substitute for MBDB and the highly selective 5-HT releasing agent MMAI (Marona-Lewicka et al., 1995). Fortunately, a recent clinical study has been conducted with human volunteers who were given 4-FA, providing the direct opportunity to learn if 4-FA produces MDMA's qualitative effects in humans (De Sousa Fernandes Perna et al., 2018; Dolder et al., 2018b; Kuypers et al., 2018b, 2019). Additionally, in 2012, the Drug Information and Monitoring System conducted a survey of drug-users who had consumed street tablets that they believed to contain only MDMA, but which in reality contained a variety of psychoactive substances (Brunt et al., 2012). They found that users who had unwittingly consumed 4-FA instead of MDMA, reported the effects to be desirable overall, and, specifically, to produce strong entactogenic effects with increased empathy, similar to what was being reported by users who had actually consumed MDMA. In a double-blind placebo controlled study, 4-FA was found to greatly enhance feelings of 'friendliness' (De Sousa Fernandes Perna et al., 2018) which one would expect from an entactogen or psychostimulant (Bershad et al., 2016). The same volunteers completed questionnaires that were interpreted by the administrators as showing that 4-FA produces a mild psychedelic state (Kuypers et al., 2019), albeit substantially milder than psychedelics such as LSD or dimethyltryptamine. The conclusion reached by these authors was that the effects of 4-FA lie between those of dextroamphetamine and MDMA, which would indicate that the term *psychedelic* may be somewhat inaccurate in describing the qualitative effects of 4-FA. On average, 4-FA reduced cognitive

empathy and did not affect emotional empathy in the 12 volunteers (Dolder et al., 2018b), which stands in contrast to MDMA, which was shown to leave cognitive empathy unaffected and to increase emotional empathy in a study using 118 volunteers (Kuypers et al., 2017). Overall, the subjective effects of 4-FA seem to be tolerated well by most users, as it was found that drug liking and drug wanting had significantly increased during the acute phase of the trial (1–3 h), but that this effect and drug wanting were absent at the 11-h mark (Kuypers et al., 2018b), indicating that 4-FA also does not exhibit significant abuse potential compared with non-halogenated amphetamines.

Like most other sympathomimetic entactogens, 4-FA caused increased systolic and diastolic blood pressure after acute administration in humans, as well as increased heart rate, approximately 5 h post administration (De Sousa Fernandes Perna et al., 2018). To date, only one study has examined the neurotoxic potential of 4-FA. 4-FA exerts its effects by entering the neuron via monoamine transporters (Fuller et al., 1975). What makes 4-FA a potentially attractive compound in clinical applications is that it seems to lack the serotonergic neurotoxicity associated with MDMA and some other entactogens. When given to rats, doses of 1.54–4.61 mg/kg, which fall within the dose-range employed in human clinical studies (De Sousa Fernandes Perna et al., 2018), did not produce any significant reduction in 5-HT and its metabolite 5-HIAA (Fuller et al., 1975). Very high doses of 15.35 mg/kg did cause short-term depletion of 5-HT and its metabolites, but these levels had returned to normal after 1 week. This makes 4-FA unique among the *para*-halogenated amphetamines, which otherwise cause significant and lasting 5-HT depletion in rats.

4-FA was shown to be a weak monoamine oxidase inhibitor in rats, and was slightly more potent at producing this effect than dextroamphetamine (Fuller et al., 1975). Some studies have been performed to measure the efficacy of 4-FA to inhibit monoamine transporters (Nugteren-van Lonkhuyzen et al., 2015) (Table 1). There is some discrepancy between the earlier literature and more recent experimental results: While all sources concluded that 4-FA potently inhibited all three monoamine transporters, earlier results using rat brain synaptosomes (Marona-Lewicka et al., 1995; Nagai et al., 2007) and HEK 293 cells (Rosenauer et al., 2012) found that DAT and NET were inhibited at about equal potencies, but that SERT was inhibited at 10-fold lower potency than the catecholamine transporters. Later studies using only HEK 293 cells reported that hSERT was inhibited least potently, with hDAT being inhibited about four times, and hNET being inhibited about 90 times, more potently than hSERT (Luethi et al., 2019). All of these studies used radio-labeled neurotransmitters. Another recent study used fluorescent neurotransmitter substitutes in HEK 293 cells, instead of radio-labelled neurotransmitters, and similarly found that the inhibition of hNET was about 110 times more potent than hSERT, but that inhibition of hDAT was about 10 times more potent than inhibition of hSERT (Rickli et al., 2015; Zwartsen et al., 2017). There are many possible reasons for these discrepancies, ranging from the different cell types used, to the fact that not all studies used radio-labeled neurotransmitters. The fact that different cell types can give significantly different results was pointed out in a study that found that hDAT inhibition of [³H]DA uptake was significantly different in wild-type compared with T356 single nucleotide polymorphism hDAT (Zwartsen et al., 2019). This polymorphism has been observed in humans (Neale et al., 2012),

and has been shown to impede the functionality of DAT (Herborg et al., 2018). Therefore, patients expressing this polymorphism may be affected differently by 4-FA than the data obtained from HEK 293 cells would imply. Regardless of their methodology, all studies agree on the following relative potency of 4-FA to inhibit monoamine transporters: hNET > hDAT > hSERT.

Some studies have also explored the ability of 4-FA to release neurotransmitters from preloaded cells (Table 1). In rat brain synaptosomes, 4-FA was found to potently induce the release of monoamines, with its ability to release [³H]NE being about twice as high as its ability to release [³H]DA, and its ability to release [³H]DA being about 20 times higher than its ability to release [³H]5-HT (Wee et al., 2005). Once again, there is some inconsistency with the older literature, where it was found that [³H]NE was released five times more potently than [³H]DA, which, in turn, was released about four times more potently than [³H]5-HT (Nagai et al., 2007). The relative potencies of [³H]NE > [³H]DA > [³H]5-HT were maintained, however. Finally, 4-FA was also found to be a partial agonist of 5-HT_{1A}, 5-HT_{2A} and 5-HT_{2C} receptors (Rickli et al., 2015).

The average dose needed to elicit entactogenic effects is reported by most users to be around 150 mg (Table 2). Users report the effects of 4-FA to be like MDMA but milder and slightly less euphoric (Supplementary file: Erowid '4-FA', 2006, (1, 4, 5, 7, 8, 9)). They also report feeling more clear-minded and slightly more stimulated than with the latter drug (Supplementary file: Erowid '4-FA', 2006, (2, 3, 4, 5, 6, 7, 8)). The effects are reported as greatly facilitating communication and increasing empathy, albeit somewhat less potently than MDMA (Supplementary file: Erowid '4-FA', 2006, (1, 2, 3, 5, 6, 8, 9)). At the above dose, the acute entactogenic effects last for 2–3 h, after which users report lower euphoria and empathy, together with residual stimulation which can last for several more hours. What users seem to value about 4-FA is that they feel that it allows them to communicate and talk openly about their feelings, while still remaining clearheaded and lucid. There seems to be less jaw tension and nystagmus present with 4-FA compared with MDMA. Users do not complain about a significant 'come down' at these doses, although this is a complaint for some users after consuming upward of 250 mg (Supplementary file: Erowid '4-FA', 2006, (3, 5, 6)). Other unwanted effects include tachycardia, increased body temperature and insomnia lasting several hours after the acute effects have worn off, due to residual stimulation (Brunt et al., 2012; De Sousa Fernandes Perna et al., 2018; Dolder et al., 2018b; Kuypers et al., 2018b; Drugs Forum '4-FA', 2004; Supplementary file: Erowid '4-FA', 2006, (2, 3, 7, 8, 9)).

Discussion

All the different chemical classes discussed in this paper share many commonalities with MDMA, while also possessing some unique qualities of their own, which are sometimes superior to those of MDMA. The qualitative effects of all these substances can be described as entactogenic, with some having effects that are difficult to distinguish from those of MDMA, while others can vary in their potency or their stimulating or euphoric effects. Once again, it must be stressed that much of the information on the qualitative effects came from anecdotal reports and should therefore be treated with appropriate caution. While such reports can, to some extent, provide a phenomenological understanding

of a compound's felt effects, the high degree of uncertainty in anecdotal reports means that they should always be followed up by structured, clinical investigations to unambiguously classify the compound's effects. In addition to their felt effects, the substances examined also show a wide range of neurotoxicity profiles, many of which are more favourable than that exhibited by MDMA. There is also a marked difference in the duration of the effects of the compounds treated here, which may be of use when careful tailoring of the duration of a therapeutic session is required.

The 1,3-benzodioxoles are natural candidates for fulfilling a role similar to that of MDMA, because, as members of MDMA's own chemical class, they share some key structural features with it and can also produce similar effects. In addition, they also contribute some unique qualities, not present in MDMA, that can be useful in their own right. MDA shares most of the desirable socioemotional sequalae of MDMA and additionally produces mild visual effects, such as closed eye visions (Baggott et al., 2010). It is also longer acting than MDMA (Table 2), which can be useful in typical drug-assisted psychotherapy sessions, as these often last longer than the acute effects of MDMA (MAPS, 2019). MDEA and MBDB are less euphoric than MDMA, and are possibly representative of more 'pure' entactogens (Nichols, 1986). Their effects are more sedating than those of MDMA, but they still produce a similar state of increased sociability, authenticity and desire to relate personal issues (Shulgin and Shulgin, 1991), which could be of use in therapeutic applications. Another benefit of MDEA and MBDB is that they seem to be less neurotoxic than MDMA (Johnson and Nichols, 1989; Schmidt, 1987), which would make them safer for repeated administration. Finally, there is evidence that enantiomerically pure preparations of these compounds may be most useful, as there seem to be some clear pharmacological and qualitative differences in the two enantiomers of MDA and MDEA (Baker and Taylor, 1997; Glennon and Young, 1984a, 1983c; Spitzer et al., 2001).

The class of substituted cathinones contains several members that could take the place of MDMA in psychotherapy. Their pharmacodynamic properties are very similar, with slightly higher selectivity for catecholamine systems over 5-HT systems compared with MDMA, and with low potency as serotonin receptor agonists (Nagai et al., 2007; Simmler et al. 2013). Their significantly lower affinity at VMAT2 and, in the case of butylone, lower efficacy for releasing neuronal catecholamines, also sets them apart from MDMA (Cozzi et al., 1999; Eshleman et al., 2013; López-Arnau et al., 2012). It is unknown whether it is these properties that contribute to the more favourable neurotoxicity profile of cathinones compared with MDMA (Anneken et al., 2015; Baumann et al., 2012). Overall, the qualitative effects of the cathinones are very similar to those of MDMA, albeit somewhat milder than the latter. Taken together, these properties indicate that methylone, butylone and ethylone could be good substitutes for MDMA, particularly in therapeutic sessions that are not intended to last as long as a typical MDMA-assisted session, or that call for an entactogen whose subjective effects are less overwhelming than those of MDMA.

The benzofurans are some of the compounds with the longest durations of action listed here, with subjective entactogenic effects that are reported to emulate those of MDMA more closely than many of the compounds from the other sections. While little is known about their long-term neurological effects, they generally seem to be tolerated better than MDMA by users. Just like MDMA, the benzofurans display a strong ability to inhibit the uptake of monoamines (Eshleman et al., 2019; Iversen et al., 2013; Shimshoni et al., 2017), as well as increase their extracellular concentrations (Fuwa et al., 2016) (Table 1). All benzofurans are also agonists at 5-HT receptors, a property they share with MDMA and MDA (Rickli et al., 2015). There are some qualitative differences in the subjective effects among the benzofurans: 5-APB and 6-APB are very powerful entactogens akin to MDMA, with the noteworthy differences of being less stimulating, and possibly mildly psychedelic at very high doses. 5-MAPB and 6-MAPB do not seem to be as psychedelic, with 5-MAPB being purely entactogenic and 6-MAPB being slightly more stimulating than the latter. 6-MAPB also shows less cardiotoxic potential than MDMA (Shimshoni et al., 2017), which could make it a useful tool in therapeutic applications where some stimulating effects are desired but where the patients involved are at greater risk of heart disease. All benzofurans share the common property that their effects last about twice as long as those of MDMA, eliminating the need to administer a second dose during prolonged therapy sessions as is usually done with MDMA (Mithoefer, 2015; Sessa et al., 2019) (Table 2).

Aminoindanes were included in this list due primarily to their seemingly safe looking neurological profile. Unlike MDMA, none of the aminoindanes that were examined produced any reduction in serotonergic markers at therapeutic doses, and both compounds fully substituted for MDMA in drug discrimination studies (Nichols et al., 1990, 1991). The aminoindanes are highly selective 5-HT modulators, both inducing the release- and preventing the re-uptake of 5-HT *in vitro* (Table 1), with 5-IAI also showing selectivity for NE systems (Eshleman et al., 2017; Halberstadt et al., 2019; Johnson et al., 1991c; Simmler et al., 2014). 5-IAI, but not MDAI, showed affinity for binding to post-synaptic 5-HT receptors (Halberstadt et al., 2019; Iversen et al., 2013). As user reports are very scarce for these substances, it is difficult to glean the exact nature of their subjective effects. In general, users report the effects as being mild, without any stimulation and very little euphoria. It is difficult to say if the euphoric effects of MDMA contribute to its therapeutic potential, for instance by inhibiting the fear responses generated by recalling traumatic memories. Some recent research indicates that MDMA's effects on DA may not be necessary for its pro-social qualities (Heifets et al., 2019), but, on the other hand, inhibiting the action of dopamine also causes subjects to experience greater anxiety from MDMA (Liechti and Vollenweider, 2000b). Nevertheless, users still report increased sociability and ease in communicating while under the influence of aminoindanes, which means that this class of drugs could serve as a tool for less intensive therapeutic sessions. For instance, a patient could receive a dose of MDMA (or some other entactogen that causes comparably strong subjective effects) during an initial 'breakthrough' session in which the patient's issues are brought forth, followed by several follow-up sessions in which the safer, less intense and non-neurotoxic aminoindanes are used to process the psychological material from the earlier session.

Finally, a cautionary note about co-administration of amphetamine with MDAI: It may be tempting to induce the euphoric component of the MDMA experience by administering the well studied and widely used stimulant dextroamphetamine, with its high selectivity for catecholamine release, alongside MDAI.

However, it was found that when non-neurotoxic doses of dextro-amphetamine were co-administered with MDAI, similar signs of serotonergic neurotoxicity were observed as with MDMA alone (Johnson et al., 1990a).

The tryptamine α-ET is unique among the compounds in this paper, not only due to its not being a phenethylamine, but also because it has a history of medical use and is a rare example of an entactogen that does not produce any stimulation and even has sedative properties. It shows high selectivity as a DA and 5-HT re-uptake inhibitor (Rényi and Ross, 1985) and releaser (Ask et al., 1989), but shows greatly reduced potency at producing the same effects with NE (Table 1). α-ET seems to have a similar effect on 5-HT neurons as MDMA, producing a similar reduction in 5-HT markers, although the study that found this used a binge-dosing regimen that does not replicate the doses given in clinical settings. Nevertheless, α-ET should probably not be treated as a less-neurotoxic alternative to MDMA, and should instead be used if entactogenic effects, lacking the stimulating effects of other entactogens, are desired. While it produces the same degree of empathy and euphoria as MDMA, α-ET does not produce any stimulation and is even reported as being somewhat sedating. This makes it particularly useful for patients who may be over-whelmed by too much stimulation or for whom stimulants may be dangerous due to pre-existing heart conditions.

The final entactogen on this list, 4-FA, is an attractive compound that seems to share the favourable neurotoxicity profile of the aminoindanes, as well as being a potent entactogen in its own right. Studies measuring the reduction of serotoneric markers brought about by the administration of *para*-halogenated amphetamines found no reduction in such markers with 4-FA (Fuller et al., 1975). Studies on the pharmacodynamics of 4-FA revealed that it displays a selectivity towards catecholamine modulation over 5-HT modulation, but still retained a far greater 5-HT releasing- and uptake-inhibiting effect than, for instance, dextroamphetamine (Luethi et al., 2019; Marona-Lewicka et al., 1995; Nugteren-van Lonkhuyzen et al., 2015; Rosenauer et al., 2012; Wee et al., 2005) (Table 1). Furthermore, 4-FA was also a partial agonist at postsynaptic 5-HT receptors, which could help explain its entactogenic effects (Rickli et al., 2015). The entactogenic effects of 4-FA lie somewhere between the effects of MDMA and dextroamphetamine (Kuypers et al., 2019), which indicates that 4-FA is less entactogenic than MDMA, although users still report a significant increase in empathy and desire to engage in conversation while under the influence of 4-FA. Indeed, some users even prefer 4-FA as an entactogen over MDMA, due to its being far more 'clear-headed' than the latter. Of all the compounds examined here, 4-FA is one of the most attractive alternatives to MDMA in that it seemingly possesses a non-toxic neurological profile but does this without sacrificing full entactogenic, MDMA-like effects. 4-FA could therefore be useful for patients requiring many psychotherapy sessions, all of which call for the aid of a fully active entactogen.

The present review also found marked gaps in our understanding of several of the compounds listed here, ranging from inadequate pre-clinical data, to a lack of clinical studies. If these compounds are to be approved for medical use, these knowledge gaps need to be filled. Specifically, the following data would be of value:

While most of the 1,3-benzodioxoles are far better studied than the other compounds on this list, MBDB still lacks clinical human data. On the other hand, MDA is already much better studied as a tool for psychotherapy than the other compounds here, and would therefore be suitable to move on to the next stage of clinical testing, in order to enable it to be approved as a medicine. In terms of *in vitro* data, while it is known that MDA is a monoamine releaser, to our knowledge, the exact EC50 values have yet to be determined. Similarly, MDEA's ability to release NE is presently unknown. Since there is some evidence that the S-isomer of MDEA produces more favourable effects (Spitzer et al., 2001), this enantiomer should be given special attention in any further work assessing neurotoxicity and therapeutic potential.

Methylone is better studied than the other two cathinones on this list, but it lacks human data from clinical trials to rigorously establish its physiological and qualitative effects. Ethylone and butylone have also not been assayed in clinical trials, but, in addition, studies investigating their neurotoxic potential are also lacking. Finally, their potency to release neuronal catecholamines has also not been measured conclusively. Butylone is often described as more stimulating than the other cathinones, which would make knowing its ability to release NE particularly interesting.

The benzofurans are perhaps the most enigmatic compounds in this review, since none of them have been tested for their neurotoxic potential, their clinical effects or their precise mechanism of action. Specifically, it would be illuminating to know if, like MDMA, they act as pseudo substrates at SERT, or if they exert their effects by an entirely different mechanism. Anecdotally, it seems like the benzofurans hold much promise as alternatives to MDMA since, together with the cathinones, their effects seem to resemble those of MDMA most closely, but, along with MDA, they are also the longest acting compounds on this list. Determining their neurological and physiological safety in humans would therefore be of great value.

The aminoindanes have been shown to be relatively safe in rodents, but no clinical studies in humans exist to date. Since their effects are reported to be somewhat milder than MDMA, the next step should be to administer these compounds to humans and directly assess their ability to produce the MDMA-like socioemotional effects needed for psychotherapy. Since it is not known if their relatively safe neurochemical effects are paralleled by mild cardiovascular effects, it would also be helpful to know to what extent aminoindanes increase blood pressure and heart rate in humans.

α-ET is already relatively well studied, and can be safely administered in a clinical setting. Nevertheless, α-ET would benefit from further research, in particular from research specifically evaluating it as an adjunct to psychotherapy, particularly for elderly patients, as it has been administered safely to this target group in the past (Pokorny, 1961). Similarly, 4-FA has already been studied in humans, but more work is needed to conclusively determine if it can serve as a suitable adjunct to psychotherapy.

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Supplemental material

Supplemental material for this article is available online.

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