1,2-Diarylethylamine- and Ketamine-Based New Psychoactive Substances

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Contents

Abstract

While phencyclidine (PCP) and ketamine remain the most well-studied and widely known dissociative drugs, a number of other agents have appeared since the late 1950s and early 1960s, when the pharmacological potential of this class was first realized. For example, hundreds of compounds have been pursued as part of legitimate research efforts to explore these agents. Some of these found

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their way out of the research labs and onto illicit markets of the 1960s and following decades as PCP analogs. Other "illicit analogs" apparently never appeared in the scientific literature prior to their existence on clandestine markets, thus originating as novel innovations in the minds of clandestine chemists and their colleagues. Like so much else in this world, new technologies changed this dynamic. In the 1990s individuals separated by vast geographical distances could now communicate nearly instantaneously with ease through the Internet. Some individuals used this newly found opportunity to discuss the chemistry and psychoactive effects of dissociative drugs as well as to collaborate on the design and development of novel dissociative compounds. Similar to modern pharmaceutical companies and academic researchers, these seekers tinkered with the structure of their leads pursuing goals such as improved duration of action, analgesic effects, and reduced toxicity. Whether all these goals were achieved for any individual compound remains to be seen, but their creations have been let out of the bag and are now materialized as defined compositions of matter. Moreover, these creations now exist not only in and of themselves but live on further as permutations into various novel analogs and derivatives. In some cases these compounds have made their way to academic labs where potential clinical applications have been identified. These compounds reached wider distribution when other individuals picked up on these discussions and began to market them as "research chemicals" or "legal highs". The result is a continuously evolving game that is being played between legislatures, law enforcement, and research chemical market players. Two structurally distinct classes that have appeared as dissociative-based new psychoactive substances (NPS) are the 1,2-diarylethylamines and β-keto-arylcyclohexylamines. Examples of the former include diphenidine and various analogs such as fluorolintane and *N*-ethyl-lanicemine, and examples of the latter are analogs of ketamine such as methoxetamine, deschloroketamine, and 2-fluoro-2-deschloroketamine. The subject of this chapter is the introduction to some of the dissociative NPS from these classes and their known pharmacology that have emerged on the market in recent years.

Keywords
Clinical · Designer drugs · Diphenidine, ketamine analogs · Dissociatives · Forensic · NMDA receptor · Pharmacology · Toxicology

Acronyms of the Discussed New Psychoactive Substances (NPS)

2-Cl-DPP (2-Cl-DPH)	1-[1-(2-Chlorophenyl)-2-phenylethyl]piperidine
2-F-DPPy	1-[1-(2-Fluorophenyl)-2-phenylethyl]pyrrolidine (fluorolintane)
2-FDCK	2-(2-Fluorophenyl)-2-(methylamino)cyclohexan-1-one
2-MK	2-(2-Methoxyphenyl)-2-(methylamino)cyclohexan-1-one
2-MXP	1-[1-(2-Methoxyphenyl)-2-phenylethyl]piperidine
2-oxo-PCA	2-Amino-2-phenylcyclohexan-1-one

2-oxo-PCE	2-(Ethylamino)-2-phenylcyclohexan-1-one
2-oxo-PCPr	2-Phenyl-2-(propylamino)cyclohexan-1-one
2-TFMDCK	2-(Methylamino)-2-[2-(trifluoromethyl)phenyl] cyclohexan-1-one
3-MeO-PCP	1-[1-(3-Methoxyphenyl)cyclohexyl]piperidine
3-MXP	1-[1-(3-Methoxyphenyl)-2-phenylethyl]piperidine
4-MeO-PV8	1-(4-Methoxyphenyl)-2-(pyrrolidin-1-yl)heptan-1-one
4-MeO-PV9	1-(4-Methoxyphenyl)-2-(pyrrolidin-1-yl)octan-1-one
4-MXP	1-[1-(4-Methoxyphenyl)-2-phenylethyl]piperidine
5F-ADB	Methyl (2*S*)-2-[[1-(5-fluoropentyl)-1*H*-indazole-3-carbonyl]amino]-3,3-dimethylbutanoate
5F-AMB	Methyl (2*S*)-2-[[1-(5-fluoropentyl)-1*H*-indazole-3-carbonyl]amino]-3-methylbutanoate
5/6-APB	1-(1-Benzofuran-5-yl)propan-2-amine or 1-(1-benzofuran-6-yl)propan-2-amine
AB-CHMINACA	*N*-[(2*S*)-1-Amino-3-methyl-1-oxobutan-2-yl]-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide
AMPA	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AMT	1-(1*H*-Indol-3-yl)propan-2-amine (α-methyltryptamine)
Br-MXE	2-(2-Bromo-5-methoxyphenyl)-2-(ethylamino) cyclohexan-1-one
DCK	2-(Methylamino)-2-phenylcyclohexan-1-one
DPE (NEDPA)	*N*-Ethyl-1,2-diphenylethanamine (ephenidine)
DPiP (NPDPA)	*N*-(1,2-Diphenylethyl)propan-2-amine
DPP (1,2-DEP)	1-(1,2-Diphenylethyl)piperidine (diphenidine)
DPPy (1,2-DEPy)	1-(1,2-Diphenylethyl)pyrrolidine
FXE	2-(Ethylamino)-2-(3-fluorophenyl)cyclohexan-1-one (fluoroxetamine)
MK-801	(+)-10,11-Dihydro-5*H*-5,10-epiminodibenzo[*a*,*d*][7] annulene (dizocilpine)
MXE	2-(Ethylamino)-2-(3-methoxyphenyl)cyclohexan-1-one (methoxetamine)
MXM (MMXE)	2-(3-Methoxyphenyl)-2-(methylamino)cyclohexan-1-one (methoxmetamine)
MXP	1-[1-(2-Methoxyphenyl)-2-phenylethyl]piperidine
PCA	1-Phenylcyclohexan-1-amine
PCE	*N*-Ethyl-1-phenylcyclohexan-1-amine
PCP	1-(1-Phenylcyclohexyl)piperidine (phencyclidine)
PV9	1-Phenyl-2-(pyrrolidin-1-yl)octan-1-one

1 Introduction

One of the terms used to describe the effects induced by phencyclidine (PCP, Fig. 1) and ketamine (Fig. 2) is "dissociative anesthetic," a term coined by Toni Domino in an effort to choose a name that describes the unique anesthetic effects of this

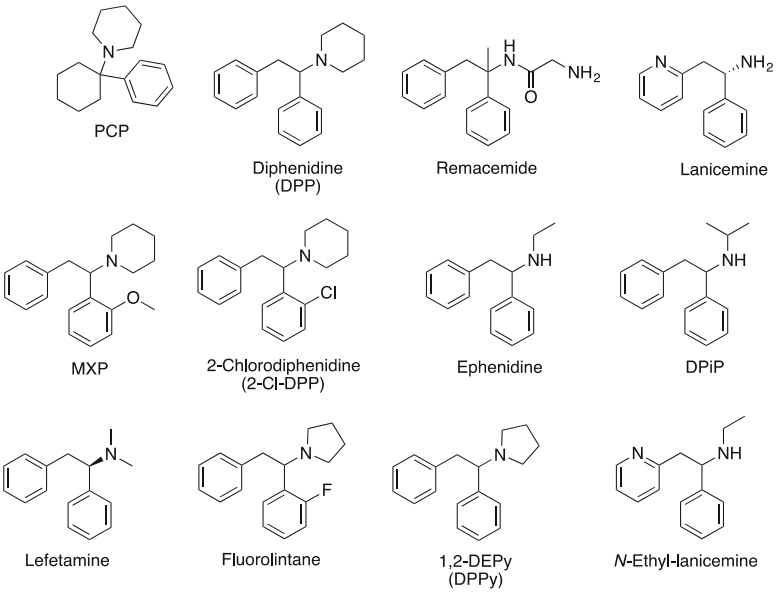

Fig. 1 Phencyclidine (PCP) and a selection of 1,2-diarylethylamines that act as NMDA antagonists. Most of these are available as research chemicals

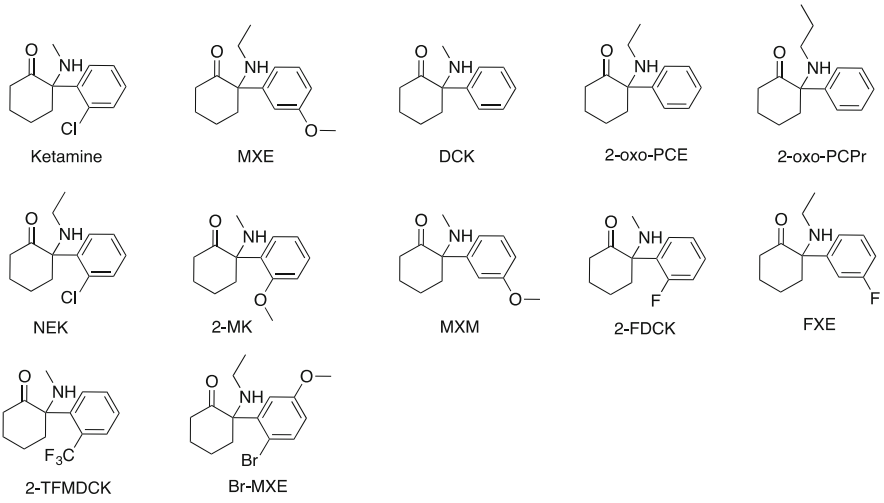

Fig. 2 Ketamine and representative ketamine analogs. Most of these are available as research chemicals

pharmacological class (Domino 2010). The term has since been abbreviated to "dissociative" to account for the wide variety of effects induced by these substances (Morris and Wallach 2014). Effects seen with dissociatives often include stimulation at lower doses with higher doses often inducing sedation, amnesia, and anesthesia.

At lower doses, the intoxication is commonly compared to ethanol and/or nitrous oxide especially. Dose-dependent perceptual alterations in all sensory modalities including visual and auditory allocations may occur. Somatosensory, proprioceptive, and tactile distortions and hallucinations are particularly common. Cognitive effects include depersonalization, derealization, and loss of ego boundaries as well as altered thought patterns, associative thoughts, ideas of reference, unusual thoughts, and, in some cases, delusions and paranoia (Pomarol-Clotet et al. 2006; Morris and Wallach 2014).

Dissociative drugs induce their unique spectrum of subjective effects likely through a shared pharmacological mechanism. While dissociative drugs interact with a number of CNS targets, it is the antagonism of the *N*-methyl-D-aspartate receptor (NMDAR) that is implicated in mediating, at least in part, the subjective and mind-altering effects of many of these compounds (Morris and Wallach 2014; Lodge and Mercier 2015). However, additional mechanisms such as inhibition of monoamine neurotransmitter transporter activity and interactions with opioid and sigma receptors may contribute to the effects of individual compounds. Users will commonly discuss the subtle differences between individual compounds, and more research is needed in this area to identify potentially relevant polypharmacology and clinically useful features.

Technology has reshaped almost every aspect of society. Drug use and recreational drug markets are no different in this respect. The Internet has played a fundamental role in the origin of, dissemination of information about, and distribution of many new dissociative research chemicals (Morris and Wallach 2014). Information exchange about the effects and circumstances of drug use can also provide opportunities for exploring harm reduction advice shared between users, at least between those who engage in online technology as recently discussed within the context of dissociative NPS use (Hearne and Van Hout 2016). Examples also exist where users of dissociative substances make clear references to self-medication and treatment (Morris and Wallach 2014), adding to speculations and discussions around the mechanisms of action associated with some of these substances and how these might affect the users' conditions (Coppola and Mondola 2012, 2013). Whether these speculations and discussions will lead to real-life clinical breakthroughs is unknown, but these reports should perhaps not be discounted. Dissociative agents have shown efficacy and potential in a wide area of therapeutic areas (e.g., Morris and Wallach 2014 and examples cited in this chapter).

Within the narrative of this chapter, dissociative NPS have been separated into two structural classes: 1,2-diarylethylamines (e.g., diphenidine, Fig. 1) and β-keto-arylcyclohexylamines (e.g., MXE, Fig. 2). Arylcyclohexylamines such as 3-MeO-PCP have been covered elsewhere (Wallach and Brandt 2018). The subject of this chapter is the introduction to some of the dissociative NPS from these classes that have emerged on the market in recent years.

2 1,2-Diarylethylamines

1,2-Diarylethylamines contain two aryl groups vicinally connected to an ethylamine side chain (Fig. 1). The 1,2-diarylethylamine template has been investigated in various areas of scientific research for several decades (e.g., Tainter et al. 1943; Dodds et al. 1945; Heinzelman and Aspergren 1953; Morris and Wallach 2014). More recently, several 1,2-diarylethylamines including remacemide and lanicemine (AZD6765) have been investigated in clinical trials where they have shown promise for use in therapeutic indications including depression, seizure, stroke, and neurodegenerative disorders (Palmer and Hutchison 1997; Zarate et al. 2013; Sanacora et al. 2014). A related compound is lefetamine which has been used as an analgesic drug (Wink et al. 2014). The structurally related compound 1-cyclohexyl-4-(1,2-diphenylethyl)piperazine (MT-45) was shown to be a potent synthetic opioid and appeared as a research chemical in its own right (WHO 2015).

The first 1,2-diarylethylamine to be sold specifically as a dissociative research chemical beginning in 2013 appears to have been diphenidine (Fig. 1) (Morris and Wallach 2014). The related compound ephenidine was reported prior to this in a 2008 seizure in Germany (Westphal et al. 2010). However, the use of ephenidine as a dissociative NPS does not appear to have occurred until early 2015. Shortly following the introduction of diphenidine, its 2-methoxy derivative methoxphenidine (MXP, 2-MXP) appeared (Morris and Wallach 2014). From the perspective of the UK market, the choice of offering 1,2-diarylethylamine research chemicals was a response to the introduction of legislation that placed substances derived from 1-phenylcyclohexanamine and 2-amino-2-phenylcyclohexanone (β-keto-arylcyclohexylamine) structural classes under legislative control in 2013 (UK S.I. No. 239 2013). This development was however foreseen by research chemical vendors who waited for legislation to enter into force followed immediately by offering diphenidine for sale. Diphenidine and other 1,2-diarylethylamines were known in the literature as NMDAR antagonists (Gray and Cheng 1989; Berger et al. 2009), and it is likely they were selected based on this property in an attempt to offer non-controlled alternatives to PCP- and ketamine-derived NPS.

2.1 Diphenidine

Diphenidine (DPP) appears to have been first synthesized in 1924 by Christiaen (1924) using a modified Bruylants reaction. Incredibly, this is the same reaction later used by V. Harold Maddox in 1956 that led to the serendipitous discovery of PCP (Morris and Wallach 2014). Other reports describing the preparation and also various analytical characterizations of diphenidine have subsequently been published (e.g., Goodson and Christopher 1950; Stewart and Hauser 1955; Le Gall et al. 2006; Hesp and Stradiotto 2010; Wallach et al. 2015; Geyer et al. 2016; Xie and Dixon 2017). Diphenidine appears to be the first 1,2-diarylethylamine dissociative research chemical to see wider distribution (Morris and Wallach 2014). Its detection was first reported to the European Monitoring Centre for Drugs and Drug Addiction

(EMCDDA) in January 2014 (EMCDDA–Europol 2015). Diphenidine induces dissociative effects at doses starting around 50–100 mg and is active by oral and parenteral routes although nasal insufflation has been described as irritating. Reports of high-dose ingestion do occur, with some describing unpleasant experiences. The duration of action has been given as 3–6 h and 2–5 h based on investigation of user reports online (Morris and Wallach 2014; Beharry and Gibbons 2016). Others have suggested common oral doses of diphenidine and the related MXP to be around 50–150 mg with duration of 3–7 h although, again, higher doses are commonly described (Helander et al. 2015).

2.1.1 Pharmacokinetics

Similar to PCP, diphenidine is a tertiary amine and weak base. Diphenidine is likewise highly lipophilic with an estimated cLogP of 5.05 (Chemdraw Ultra). For comparison, the LogP of PCP is 5.1 (Kamenka and Geneste 1981). Consistent with this, high distribution has been seen into adipose tissue of postmortem samples. For example, diphenidine was detected in blood, urine, and several solid tissues in an autopsy of a fatal case involving diphenidine and synthetic cannabinoid receptor agonists 5-F-AMB and AB-CHMINACA. Eight solid tissues were analyzed in this study including the adipose tissue, brain, heart muscle, liver, kidney, spleen, lung, and pancreas. The highest concentration of diphenidine (11,100 ng/g) was detected in adipose tissue (Hasegawa et al. 2015). Diphenidine has also been detected in hair samples 49 days following single administration (123, 79, and 89 pg/mg in first three proximal segments) (Alvarez et al. 2017), whereas the detection of 4,400 pg/mg was reported in another study (Salomone et al. 2016).

The metabolic transformation of diphenidine has been investigated using CYP450 isozyme preparations, pooled human liver microsomes, and cytosol and following administration to rats (male Wistar) for urinalysis (Wink et al. 2016). Mono- and bis-hydroxyl and oxo-piperidine metabolites were detected using the human liver preparations. CYP1A2, CYP2B6, CYP2C9, and CYP3A4 were found to be capable of catalyzing formation of the hydroxy-aryl, hydroxy-piperidine, and bis-hydroxypiperidine metabolites, whereas CYP2D6 produced hydroxy-aryl and hydroxy-piperidine metabolites. In rat urine, the major phase I metabolites detected were those resulting from mono- and bis-hydroxylation, dehydrogenation, oxo-piperidine, *N*,*N*-bis-dealkylation, and various combinations of these. Phase II metabolites included glucuronide conjugates of the phase I metabolites and/or methylation of one of the bis-hydroxy-aryl groups (Wink et al. 2016).

Diphenidine and the hydroxyl-piperidine diphenidine metabolite were detected at trace concentrations in a fatal intoxication case associated with MXP although it was not possible to discern whether these derived from MXP transformation or whether this was a reflection of diphenidine co-ingestion (Elliott et al. 2015). Two major metabolites detected in blood and urine in a fatal case involving diphenidine were those resulting from mono-hydroxylation of the piperidine ring and mono-hydroxylation of a phenyl ring. Dihydroxy-dehydrogenated as well as dihydroxylated metabolites (positions not determined but dehydrogenation appeared to occur mainly on the piperidine ring) were also detected (Minakata et al. 2015).

Mono- and dihydroxy metabolites of diphenidine, involving the piperidine and both phenyl rings, were detected in blood and urine from a fatal case involving diphenidine and the synthetic cannabinoid receptor agonist 5F-ADB (Kusano et al. 2017).

2.1.2 Pharmacodynamic Effects In Vitro

Diphenidine has been found to have high affinity for the PCP binding site of NMDAR (Wallach et al. 2016; Gray and Cheng 1989; Berger et al. 2009) (Table 1). Diphenidine contains a stereogenic carbon center and is thus chiral containing two enantiomers. In two studies, large differences in NMDAR affinity were reported between diphenidine enantiomers, with (+)-(*S*-)-diphenidine showing substantially higher affinity than the (−)-(*R*-) enantiomer (Table 1) (Gray and Cheng 1989; Berger et al. 2009). Diphenidine acts as an NMDAR antagonist likely through an uncompetitive channel-blocking effect as it was found to block NMDAR-mediated field excitatory postsynaptic potentials (fEPSPs) in rat hippocampal slices (1 and 10 μM) in a manner consistent with a channel blocker. In addition to diphenidine, a number of related compounds and known NMDAR antagonists were recently evaluated for effects on NMDAR-mediated fEPSPs. The rank order of potency for inhibition was found to be MK-801 > PCP > 2-Cl-DPP ≥ DPP ≥ 3-MXP ≥ 2-MXP > ketamine > 4-MXP ≥ memantine, which closely paralleled NMDAR affinities (Wallach et al. 2016).

Diphenidine showed affinities for (Table 1) and exhibited reuptake inhibition properties at human monoamine transporters NET and DAT in transfected HEK293 cells (IC_{50} = 9,250 and 1,990 nM, respectively; SERT IC_{50} > 10,000 nM) (Wallach et al. 2016). Similar results (Table 1) were reported by Luethi et al. (2018) using comparable methods (NET IC_{50} = 3,300 nM, DAT IC_{50} = 3,400 nM, SERT IC_{50} = 675 μM) (Luethi et al. 2018). However, diphenidine did not cause monoamine ([^{3}H]NA, [^{3}H]DA, or [^{3}H]5-HT) efflux in the same transporter-transfected HEK293 cells (Luethi et al. 2018). In addition to activity at NMDAR and monoamine transporters, diphenidine showed low μM affinities at human 5-HT receptor subtypes (5-HT_{1A} and 5-HT_{2A}), alpha-adrenergic receptor subtypes (α_{1A}, α_{2A}, α_{2B}, and α_{2C}), various histamine receptor subtypes, muscarinic subtypes, and the kappa opioid receptor (KOR) with some differences between studies (Wallach et al. 2016; Luethi et al. 2018). Diphenidine also showed affinity for sigma-1 (K_i = 290 nM) and sigma-2 receptors (K_i = 193 nM) (Wallach et al. 2016). Finally, diphenidine lacked notable affinity (>15 μM) at rat and mouse trace amine-associated receptor one (TAAR-1) in transfected HEK293 cells (Simmler et al. 2016). As monoamine reuptake inhibition and the other effects discussed are reduced in potency relative to NMDAR antagonism, their contribution to the drug effects of diphenidine is unclear, although a contribution, particularly in cases of high doses or overdoses, cannot be excluded.

Table 1 Receptor binding affinities of 1,2-diarylethylamines at key CNS receptor sites

Compound	NMDAR	NET	DAT	SERT
Diphenidine	$K_i = 18.2$ nM Wallach et al. (2016) $K_i = 39$ nM Gray and Cheng (1989)	$K_i = 2{,}808$ nM Wallach et al. (2016) $K_i = 3{,}400$ nM Luethi et al. (2018)	$K_i = 317$ nM Wallach et al. (2016) $K_i = 230$ nM Luethi et al. (2018)	$IC_{50} > 10{,}000$ nM Wallach et al. (2016) $K_i = 27$ μM Luethi et al. (2018)
(+)-(*S*)-DPH	$K_i = 130$ nM Berger et al. (2009) $K_i = 25$ nM Gray and Cheng (1989)			
(−)-(*R*)-DPH	$K_i = 5{,}250$, 7,020 nM Berger et al. (2009) $K_i = 2{,}900$ nM Gray and Cheng (1989)			
2-MXP	$K_i = 36$ nM Wallach et al. (2016) $K_i = 170$ nM Gray and Cheng (1989)	$IC_{50} > 10{,}000$ nM Wallach et al. (2016) $K_i = 6{,}900$ nM Luethi et al. (2018)	$K_i = 2{,}915$ nM Wallach et al. (2016) $K_i = 4{,}800$ nM Luethi et al. (2018)	$IC_{50} > 10{,}000$ nM Wallach et al. (2016) $K_i = 20$ μM Luethi et al. (2018)
Ephenidine	$K_i = 66$ nM Kang et al. (2017) $K_i = 257$ nM Thurkauf et al. (1989)	$K_i = 841$ nM Kang et al. (2017)	$K_i = 379$ nM Kang et al. (2017)	$IC_{50} > 10{,}000$ nM Kang et al. (2017)

Radioligands and tissue preparations used for NMDAR binding: Wallach et al. (2016) and Kang et al. (2017) [^{3}H]MK-801 in rat forebrain. Gray and Cheng (1989) [^{3}H]TCP in whole rat brain. Radioligands and tissue preparations used for DAT, NET, and SERT: Luethi et al. (2018), Wallach et al. (2016), and Kang et al. (2017). Radioligands: *N*-methyl-[^{3}H]nisoxetine (NET), [^{3}H] WIN35,428 (DAT), [^{3}H]citalopram (SERT) in HEK293 cells transfected with human transporters *NMDAR* *N*-methyl-D-aspartate receptor, *NET* norepinephrine transporter, *DAT* dopamine transporter, *SERT*, K_i inhibitory constant, IC_{50} half maximal inhibitory constant

2.1.3 Effects In Vivo

Diphenidine significantly disrupted pre-pulse inhibition (PPI) in male Sprague-Dawley rats ($ED_{50} = 9.5$ mg/kg, sc) (Wallach et al. 2016). In comparison, PCP, (*S*)-ketamine, and (*R*)-ketamine were found to have ED_{50} values of 0.88, 2.86, and 6.33 mg/kg, sc for PPI disruption in the same model, respectively (Halberstadt et al. 2016). PPI is a measure of sensorimotor gating, and inhibition of PPI is seen with other NMDAR antagonists in rats and is believed to be predictive of dissociative effects in humans (Halberstadt et al. 2016). The reduced potency of diphenidine

(as well as that of MXP) relative to PCP and ketamine is notable given the high affinity for NMDAR seen (Table 1) and suggests that possible pharmacokinetic effects might influence the potency of 1,2-diarylethylamines in vivo. The reduced potency in PPI is consistent with reports of relatively low potency in humans with common doses of diphenidine around 50–100 mg (see above). The reason for the reduced potency relative to NMDAR affinity warrants further study. Other behavioral effects have been reported with diphenidine. For example, stereotypy was induced in male Sprague-Dawley rats following three different routes of administration: intracerebroventricular (icv, ED_{50} = 220 nmol/rat vs. PCP = 150 nmol/rat), subcutaneous (sc, ED_{50} = 2.9 mg/kg vs. PCP not tested), and intraperitoneal injection (ip, ED_{50} = 2.0 mg/kg vs. PCP not tested). Interestingly, the (+)-(*S*)-enantiomer was more potent in eliciting stereotypic behavior using two of the three routes of injection (icv, ED_{50} = 120 nmol/rat; sc, ED_{50} = 0.78 mg/kg; ip, ED_{50} = 2.1 mg/kg) consistent with a slightly higher NMDAR affinity compared to the racemate (Table 1). In contrast, the ED_{50} for the (+)-(*R*)-enantiomer of diphenidine was given as >40 mg/kg (sc) (Gray and Cheng 1989).

2.1.4 Clinical Toxicology

In the period between January and December 2014, 14 hospitalizations in Sweden were reported to involve diphenidine and 3 involved MXP (see section below). Diphenidine concentrations ranged from 2 to 262 ng/mL (mean 88.4 ng/mL) in serum and between 8 and 19,000 ng/mL (mean 2,213 ng/mL) in urine. In all but two cases, other substances were detected in urine and/or blood. Common clinical features of intoxication with diphenidine and/or MXP included hypertension (76%), tachycardia (47%), anxiety (65%), and altered mental status (65%) including confusion, disorientation, dissociation, and/or hallucinations. Nystagmus (24%), meiosis (35%), and muscle rigidity (24%) were also reported (Helander et al. 2015). A recent case involving a diphenidine intoxication in a 30-year-old male was described in which the patient exhibited "agitation, disorientation and altered consciousness state," tachycardia, increased respiration, miosis, muscle rigidity, and signs of metabolic acidosis and rhabdomyolysis. This patient was hospitalized after being found in a "confused and agitated state" and was unable to communicate. Diphenidine concentrations in plasma and urine were 308 and 631 ng/mL, respectively (methylphenidate and diclazepam were also found in plasma) (Gerace et al. 2017). A fatal intoxication of a 53-year-old male involving the synthetic cannabinoid receptor agonist 5F-ADB and diphenidine was reported in 2017. Postmortem blood concentrations (right heart) were found to be 12 ng/mL for diphenidine and 0.19 ng/mL 5F-ADB (Kusano et al. 2017). In an autopsy case of a 30-year-old male, analyses of various tissue and biofluid samples obtained revealed the detection of AB-CHMINACA, 5F-AMB, and diphenidine. Whereas the first two drugs were not detected in femoral and heart blood and urine (but other tissues, e.g., the brain, adipose tissue, and others), the diphenidine concentration was determined at 715 ng/mL in femoral blood (right heart blood, 707 ng/mL; left heart blood, 923 ng/mL; urine, 376 ng/mL). Moreover, adipose tissue revealed a particularly high diphenidine concentration of 11,100 ng/g, the highest of all tissues analyzed (Hasegawa et al. 2015). The same case samples were analyzed using an alternative analytical

technique, which revealed diphenidine concentrations in blood (right atrium) and in urine of 726 and 304 ng/mL (Minakata et al. 2015). Another fatal case was reported involving diphenidine, three synthetic cathinones, ethanol, and therapeutic concentrations of benzodiazepines in Japan involving a female individual in her 30s. The concentrations of 4-MeO-PV8, PV9, 4-MeO-PV9, and diphenidine detected in femoral blood were 2,690, 743, 261, and 1,380 ng/mL, respectively. The only findings reported included pulmonary congestion and edema (Kudo et al. 2015). A death involving a female in her 20s associated with multiple drug intoxication was reported to involve the detection of 7-aminoflunitrazepam, 7-aminonimetazepam, chlorpheniramine, and diphenidine in femoral blood at concentrations of 86, 27, 66, and 73 ng/mL, respectively. Congestion and edema were reported (Kinoshita et al. 2017).

2.2 MXP

Shortly following diphenidine, MXP (2-MXP, methoxphenidine) was the second 1,2-diarylethylamine dissociative to become widely available as a research chemical and its history has been described previously (Morris and Wallach 2014). Syntheses and analytical characterizations related to MXP and positional isomers have been described (e.g., Taschwer et al. 2014; McLaughlin et al. 2016; Geyer et al. 2016; Xie and Dixon 2017; Boateng et al. 2018). MXP is psychoactive via oral and parenteral routes although nasal insufflation, similar to diphenidine, has been reported to be unpleasant. Based on reviews of online posts, active doses were reported to start around 30–50 mg with doses of greater than 150 mg being described as strong. The duration of action of MXP has been described as between 6–8 h (Beharry and Gibbons 2016) and 3–7 h (and/or diphenidine; Helander et al. 2015). An evaluation of Internet forum posts suggested that a number of users reported MXP as more pleasurable than diphenidine, with one user calling it an "absolute gem of a chem." Many users appeared to prefer the oral route of ingestion, although other routes were also described (im, intranasal, rectal (plugging), sublingual, and smoking). Doses described generally ranged from 30 to 80 mg although reports of high doses in the hundreds of mg were described. Onset was reported to occur in 30–60 min (dependent on a number of factors including dose, tolerance, and route of administration). Some users described long-lasting and cumulative psychoactive effects with repeated dosing speculating this might have been due to a long half-life. Of note is that a number of users reported interest in the therapeutic use of MXP as a "life enhancer" and antidepressant (Van Hout and Hearne 2015). Desirable effects included stimulant and dissociative effects, euphoria, introspection, out-of-body experiences, auditory and visual hallucinations, enhanced tactile sensations, kinesthetic effects, and spatial distortion. Negative side effects reported included "physical sensations of chest pain, palpitations, facial flushing, cold extremities, respiratory difficulties, hyperthermia, and spasms." Some users also reported incidences of urinary retention, hypertension, and seizures. Cognitive impairment, muscle cramps, and "numbness in left-side extremities" were also described by some users to last several days following ingestion (Van Hout and Hearne 2015).

2.2.1 Pharmacokinetics

Systematic studies investigating the metabolism of MXP have not been published so far. Investigations of biofluids derived from fatal intoxication cases associated with MXP uncovered the detection of hydroxy-MXP (piperidine ring) as the main metabolite in blood and urine. *O*-Demethyl-MXP and hydroxyl-*O*-demethyl-2-MXP (piperidine ring) were also detected. Notably, diphenidine and hydroxy-diphenidine (piperidine ring) were reported in what appeared to be trace concentrations in these cases although it was not possible to determine whether these resulted from metabolism of MXP or from ingestion of diphenidine as a separate substance (Elliott et al. 2015). Hydroxy-MXP, dihydroxy-MXP, and hydroxyl-demethyl-MXP metabolites (position of hydroxylation undetermined) were also detected in urine of a 35-year-old man who was hospitalized resulting from MXP intoxication (Lam et al. 2016). Three hydroxylation products, *O*-demethyl-MXP, and three glucuronidated hydroxylation products (positions of modifications not specified) were detected in a urine sample collected from an acute intoxication case (Hofer et al. 2014). In all cases (Hofer et al. 2014; Lam et al. 2016; Elliott et al. 2015), prescription medicines were also detected.

2.2.2 Pharmacodynamic Effects In Vitro

MXP was found to be a high-affinity NMDAR antagonist (Kang et al. 2017; Wallach et al. 2016; Gray and Cheng 1989; Berger et al. 2009) (Table 1). Correspondingly, MXP blocked NMDAR-mediated fEPSPs in rat hippocampal slices (1 and 10 μM) with no effect on AMPA receptor-mediated fEPSPs at 50 and 100 μM (Wallach et al. 2016). The 3- and 4-MeO isomers of MXP have also been investigated. Interestingly, the rank order of potency for NMDAR affinity followed the same pattern seen with arylcyclohexylamines (3-MeO- > 2-MeO- > 4-MeO-) suggesting overlapping structure activity relationships of the benzylpiperidine moieties between arylcyclohexylamines and 1,2-diarylethylamines (Gray and Cheng 1989; Wallach 2014; Wallach et al. 2016). Remarkably, 2-Cl-DPP was found to have the highest NMDAR affinity of the five 1,2-diarylethylamines tested consistent with an earlier study from a patent (Gray and Cheng 1989; Wallach et al. 2016). MXP showed affinities (Table 1) and reuptake inhibition at human monoamine transporters NET (IC_{50} = 35.2 μM, IC_{50} = 7,800 nM) and DAT (IC_{50} = 30 μM, IC_{50} = 65 μM) expressed in HEK293 cells (Wallach et al. 2016; Luethi et al. 2018). Significantly reduced effects were reported at SERT (IC_{50} > 10,000 nM, IC_{50} = 741 μM) (Wallach et al. 2016; Luethi et al. 2018). The low activity at SERT relative to DAT and NET was observed with five 1,2-diarylethylamines evaluated including diphenidine, 2-MXP, 3-MXP, 4-MXP, and 2-Cl-DPP. 3-MXP had the highest affinities (K_i = 88 and 325 nM, respectively) and inhibition potencies (IC_{50} = 587 and 2,710 nM) at DAT and NET, of the series (Wallach et al. 2016). Interestingly, explorations of the *N*-(1,2-diphenylethyl)piperazine template including substituents at both the benzyl ring and phenyl ring gave rise to monoamine reuptake inhibitors with selectivity for serotonin and norepinephrine over dopamine transporters (Fray et al. 2006a, b). As with diphenidine, MXP did not cause monoamine ([^{3}H]NA, [^{3}H]DA, or [^{3}H]5-HT) efflux in monoamine transporter-transfected HEK293 cells

(Luethi et al. 2018). Although some discrepancies exist between the two studies, MXP showed low μM affinities for 5-HT receptor subtypes (5-HT_{2A} and 5-HT_{2c}), α-adrenergic receptor subtypes (α_{2A}), histamine receptor subtypes, muscarinic subtypes, and KOR (Wallach et al. 2016; Luethi et al. 2018). Affinities for sigma-1 (K_i = 124 nM) and sigma-2 (K_i = 508 nM) were also seen for MXP (Wallach et al. 2016), and MXP lacked significant affinity (>15 μM) at rat and mouse trace amine-associated receptor one (TAAR-1) (Simmler et al. 2016).

2.2.3 Effects In Vivo

Similar to diphenidine and other NMDAR antagonists, MXP (20 mg/kg, sc) significantly disrupted PPI in male Sprague-Dawley rats albeit with lower potency than diphenidine (ED_{50} = 9.5 mg/kg, sc). MXP was also less potent in these PPI experiments compared to PCP and ketamine (Halberstadt et al. 2016), which was unexpected based on its high NMDAR affinity, although this was consistent with reduced potency in humans and the same can be said for diphenidine (Wallach et al. 2016).

2.2.4 Clinical Toxicology

What appeared to be the first published fatal cases associated with MXP appeared in 2015, which also included the differentiation between three positional isomers 2-, 3-, and 4-MXP. In the first case, a 34-year-old male, the cause of death was ruled as MXP use and hypertensive heart disease. Mirtazapine, lamotrigine, and citalopram were also detected at therapeutic concentrations. In the second case, a 34-year-old male, diazepam and quinine were also detected. In the absence of other pathological findings, the cause of death was given as "probable methoxyphenidine toxicity." In the third case, a 38-year-old male, risperidone was also detected at a therapeutic concentration, and the cause of death was due to fatal injuries sustained from a fall. MXP concentrations in femoral blood were found to be 24,000, 2,000, and 1,360 ng/mL, respectively (Elliott et al. 2015, 2018).

As described in the diphenidine section, a number of cases involving MXP intoxication were described in Sweden as part of the STRIDA project (Jan–Dec 2014). MXP concentrations were reported to range from 187 to 409 ng/mL in serum and 3 to 8,367 ng/mL (median 610 ng/mL) in urine. The clinical features were consistent with those described above in the diphenidine section (Helander et al. 2015).

A case of MXP intoxication involving a 53-year-old male has been reported. He was found in a "somnolent and confusional state." Reported signs and symptoms included miosis, tachycardia, hypertension, echolalia, confusion, agitation, opisthotonus, nystagmus, and amnesia. This patient was also taking a large number of prescription and non-prescription drugs, which might have contributed to the observed clinical features. MXP was identified qualitatively in plasma and urine (Hofer et al. 2014).

A 35-year-old male, with a history of hypothyroidism, Wolff-Parkinson-White syndrome, adjustment disorder, and alcohol dependence and who had ingested MXP, was found somnolent in the street. He exhibited retrograde amnesia, hypertension (179/95 mmHg), slurred speech, mild hypokalemia, as well as elevated

alanine amino transferase, aspartate aminotransferase, and lactate dehydrogenase levels. In addition, severe rhabdomyolysis (considered multifactorial) and acute kidney injury were noted. MXP (qualitative detection), a methylphenidate metabolite, tramadol, and lorazepam were detected in urine (Lam et al. 2016).

A case report involving the drowning of a 21-year-old male in a bathtub associated with multidrug exposure revealed the detection of lorazepam (5.7 ng/mL), delorazepam (54 ng/mL), amphetamine (64 ng/mL), 4-fluoroamphetamine (2.1 ng/mL), and MXP (190 ng/mL) in femoral blood. Blood alcohol concentration was determined to be 0.93‰ (Grumann et al. 2016).

A 21-year-old male with a history of drug use and bipolar I disorder was hospitalized due to agitation and aggressiveness following regular, self-reported use of MXP. Analytical data recorded from biofluids were not available apart from the confirmation of MXP in the patient's drug sample. Over the course of hospitalization, the authors suggested that the patient might have suffered from withdrawal symptoms (including abdominal pain, vomiting, and low-grade fever (38°C) without infectious diseases) (Champeau et al. 2017).

Unexpected clinical features mimicking an ischemic cerebral disease were observed in a 25-year-old male who presented with the inability to maintain the upright position and exhibited referred hyposthenia at lower limbs after an episode of syncope with secondary head trauma. The patient was described as exhibiting excitatory behavior, psychomotor agitation, confusion, dysarthria, and aphasia. Mild hypertension (150/100 mmHg), heart rate (85 bpm), and a body temperature of 36.5°C were also described. MXP and flubromazepam (NPS benzodiazepine) concentrations in blood were determined at 247 ng/mL and 411 ng/mL, respectively (Valli et al. 2017).

A severe serotonin syndrome was described in a 33-year-old autistic male who ingested one or more tablets containing MXP and tryptamine-based hallucinogen AMT (Chretien et al. 2018). He was found in a state of severe agitation and hospitalized at which point he presented with profuse sudation, hyperthermia, tachycardia (140 bpm), and mydriasis. A Glasgow Coma Score of 10/15 was determined. He also was reported to have hypercapnic acidosis, elevated lactates, renal dysfunction, and rhabdomyolysis. Effects induced by AMT (including inhibition of monoamine oxidase) increase the risk of serotonergic toxicity (Elliott et al. 2013). This patient's "usual treatment" included methadone, loxapine, and lorazepam, which were also detected as were several other substances including mirtazapine, amantadine, and nortriptyline (Chretien et al. 2018)

A 32-year-old male with a history of psychosis and multi-substance use disorder including self-reported use of various dissociative drugs including MXP was hospitalized for treatment of psychotic disorder although it was not specified whether MXP use was detected in biofluids (Caloro et al. 2018).

2.3 Ephenidine

Ephenidine (NEDPA or DPE) was detected in a confiscated sample in Germany in 2008 (Westphal et al. 2010). As stated previously, the availability of ephenidine as a dissociative research chemical, at least based on sale from online retailers or discussion of use on drug forums, did not appear to occur until around 2014 (Beharry and Gibbons 2016). The synthesis and analytical characterization of ephenidine has been reported (Goodson et al. 1946; Campbell et al. 1948; Goodson and Christopher 1950; Novelli and Huidobro 1963; Marcsekova et al. 2005; Garcia Ruano et al. 2009; Kang et al. 2017; Xie and Dixon 2017). Ephenidine has been reported to be an active dissociative through oral and parenteral routes with doses in the 10–100s of mg range, with a threshold dose given as 60 mg. Doses over 200 mg were considered "heavy" according to users on discussion forms. The onset has been said to be slow by some users especially with oral ingestion, and the duration of effects have been reported to be around 5–7 h although higher doses may result in longer duration. Users seem to like the effects and in some cases more so than some other dissociatives (Beharry and Gibbons 2016). The related *N*-(1,2-diphenylethyl) propan-2-amine (NPDPA or DPiP) was also detected along with ephenidine in confiscated samples in Germany in 2008 (Westphal et al. 2010). Currently, DPiP does not appear to be available as a research chemical.

2.3.1 Pharmacokinetics

The metabolism of ephenidine and DPiP was investigated in male Wistar rats using urinalysis. The phase I metabolic transformations detected in urine included *N*-dealkylation (leading to the same primary amine metabolite, 1,2-diphenethylamine (DPA)), mono- and bis-aryl-hydroxylation on the benzyl ring, and combinations of these. Phase II metabolites included glucuronidation, methylation, and sulfation of phase I metabolites (Wink et al. 2014). Further work carried out by Wink et al. established the contributions from ten human CYP450 isozymes to the *N*-dealkylation of ephenidine, DPiP, and lefetamine. For ephenidine net clearances were calculated using a relative activity factor approach as follows: 27% (CYP1A2), 30% (CYP2B6), 23% (CYP2C19), 4% (CYP2D6), and 17% (CYP3A4) (Wink et al. 2015). The net clearances calculated for the *N*-dealkylation of DPiP were found to be 18% (CYP1A2), 24% (CYP2B6), 28% (CYP2C19), and 30% (CYP3A4). For lefetamine, the values were 8% (CYP1A2), 72% (CYP2B6), 2% (CYP2C19), 1% (CYP2D6), and 17% (CYP3A4) (Wink et al. 2015). Ephenidine and DPiP have also been evaluated for substrate activity at the human efflux transporter P-glycoprotein (Pgp). A K_m value of 4.6 μM was determined for DPiP, whereas ephenidine lacked substantial substrate activity at concentrations as high as 500 μM (Meyer et al. 2013b).

2.3.2 Pharmacodynamic Effects In Vitro

Ephenidine has high-to-modest affinity at the PCP binding site of NMDAR (Table 1) in rat brain labeled by [^{3}H]MK-801 (Thurkauf et al. 1989 (details not reported); Kang et al. 2017). NMDAR antagonism was observed through blockade of

NMDAR-mediated fEPSPs in rat hippocampal slices at 1, 10, and 30 μM. No effect on AMPA receptor-mediated fEPSPs at 50 μM was demonstrated consistent with MXP (Kang et al. 2017, Wallach et al. 2016). Voltage-dependent NMDAR blockade for ephenidine was found to be similar to ketamine, memantine, MK-801, and Mg^{2+} where outward currents were less affected than inward. Specifically, ephenidine reduced inward current at negative holding potentials consistent with a channel blocker effect. Ephenidine had a rectification index, between that of Mg^{2+} and ketamine (Kang et al. 2017). Importantly, the voltage dependency of NMDAR blockage has been related to therapeutic potential (Frankiewicz et al. 1996). Ephenidine also had a slower onset of NMDAR fEPSP blockade compared to ketamine at equivalent concentrations in this study (Kang et al. 2017). This slower onset was seen with other 1,2-diarylethylamines tested as well as MK-801 and PCP and is suggestive of altered blocking kinetics relative to ketamine (Wallach et al. 2016). Consistent with other NMDAR antagonists (Frankiewicz et al. 1996), ephenidine blocked long-term potentiation induction induced by theta burst stimulation at 10 μM in CA1 region of rat hippocampal slices (Kang et al. 2017). Similar to several related 1,2-diarylethylamines, ephenidine was observed to have modest affinities at human monoamine transporters DAT and NET but not SERT expressed in HEK293 cells (Table 1) (Kang et al. 2017). Modest affinity was also seen for sigma-1 and sigma-2 receptors (K_i = 629 and 722 nM, respectively) (Kang et al. 2017). The *N*-dealkylation metabolite, DPA, has been reported to have modest affinity for NMDAR (K_i = 690 nM) (Thurkauf et al. 1989) and therefore could contribute to the pharmacological effects of ephenidine.

2.3.3 Effects In Vivo

Along with a number of related 1,2-diarylethylamines, ephenidine was evaluated for its sympathomimetic and bronchodilating properties. In dogs (5–15 mg/kg, iv), ephenidine produced "a fall in blood pressure, which was sometimes followed by a rise of 20–30 mmHg" (details not reported). Low-potency stimulant properties were observed as defined by an increase in spontaneous activity in "white rats" following subcutaneous administration. The threshold dose for ephenidine was 8 mg/kg (compared to 0.25 mg/kg for (*S*)-amphetamine), whereas the maximum peak effect was observed at 128 mg/kg compared to a dose of 2 mg/kg of (*S*)-amphetamine that also displayed twice the response at the maximum dose in terms of spontaneous activity (Tainter et al. 1943). Ephenidine was also part of a series of 1,2-diarylethylamines evaluated in the mid-1940s for analgesic activity in mice although details on the results were not included (Goodson et al. 1946). In an in vivo model used to evaluate potential dopaminergic anti-Parkinson effects (Sprague-Dawley rats lesioned unilaterally with 6-hydroxydopamine in the nigrostriatal system), ephenidine was inactive at a dose of 320 μmol/kg (ip), whereas some aminotetralin derivatives did show dopaminergic effects under these conditions (Cheng et al. 1976). An LD_{50} value in white rat (iv) was determined for ephenidine to be 55 mg/kg (Tainter et al. 1943). In a clinical study in cancer patients with intractable pain, DPA was given orally (200 mg, 3 h intervals) and found to display analgesic properties. However, mental confusion developed after about 1 h.

In healthy subjects, similar doses were reported to produce elation and slight muscular incoordination comparable to effects induced by ethanol. Most patients refused receiving DPA again after receiving a series of doses. Interestingly, the β-hydroxy derivative of DPA (2-amino-1,2-diphenylethanol) (200–400 mg, 4-hourly, po) provided complete pain relief in 14 patients without undesirable side effects (Dodds et al. 1944). As part of a study to evaluate anorectic properties, DPA, among other ring-substituted 1,2-diphenylethan-1-amine analogs, reduced food intake in female Sprague-Dawley rats (ip) without significantly affecting motor activity (Ghosh et al. 1978).

2.3.4 Clinical Toxicology

No reports associated with ephenidine intoxication or fatal overdoses could be identified.

2.4 Other 1,2-Diarylethylamines

2.4.1 Fluorolintane

Fluorolintane appears to have first been marketed as a research chemical around 2015, and limited information available from online posts indicate that fluorolintane might show dissociative effects, for example, at doses from 100–400 mg with a 2–4 h duration. Stimulating effects at 100 mg were also mentioned (Anonymous 2015b). Some analytical data are available in the public domain (National Slovenian Forensic Laboratory 2016), and the synthesis of fluorolintane has been recently described (Xie and Dixon 2017). While fluorolintane appears to have emerged as a novel research chemical recently with no pharmacological data reported in the scientific literature, the defluoro analog of fluorolintane (DPPy, Wallach et al. (2015)), which is also the pyrrolidine analog of diphenidine (DPP), has been prepared and investigated for a variety of potential clinical applications (e.g., Heinzelman and Aspergren 1953; Aspergren and Heinzelman 1963, 1964; Kasé et al. 1963; Yuizono et al. 1970). The reported affinity of DPPy for NMDAR was surprisingly low (K_i = 16,000 nM) (Gray and Cheng 1989), which suggests that further studies are warranted to confirm this finding.

2.4.2 *N*-Ethyl-Lanicemine

One of the more recent 1,2-diarylethylamines sold as a research chemical is *N*-ethyl-lanicemine (Fig. 1). This compound is the *N*-ethyl derivative of lanicemine (AZD6765), a low-trapping NMDAR antagonist (K_i = 0.56–2.1 μM) developed by AstraZeneca and which has been investigated clinically for depression (Zarate et al. 2013; Sanacora et al. 2014; Machado-Vieira et al. 2017). At doses up to 150 mg, lanicemine showed antidepressant effects in treatment-resistant major depressive disorder in randomized trials with minimal dissociative effects (Zarate et al. 2013; Sanacora et al. 2014). By contrast, *N*-ethyl-lanicemine was shown to be a high-trapping NMDAR antagonist, using whole cell recordings in cultured rat cortical neurons, which was suggested to "produce significant amounts of

PCP-like behaviors in rats at lower doses" (Mealing et al. 2001). It is likely that *N*-ethyl-lanicemine might have dose-dependent dissociative effects in humans, but further research is needed to confirm this. A sample of material sold as *N*-ethyl-lanicemine was tentatively identified using mass spectrometry (HR-MS, GC-MS) and NMR (Wallach, Dybek and Brandt unpublished).

3 β-Keto-Arylcyclohexylamines

β-Keto-arylcyclohexylamines contain a ketone function in the respective 2-position (or β-) of the cyclohexyl ring of arylcyclohexylamines. The contribution of the β-keto group to the structure-activity relationships of these compounds relative to their arylcyclohexylamine counterparts remains largely unpublished, and it is hoped that this situation will change with increased interest in this area.

3.1 History

A patent application initiated by the Parke-Davis pharmaceutical company in 1957 described the synthesis of 2-oxo-PCA as an intermediate to prepare the arylcyclohexylamine PCA (Anonymous 1960). In a 1962 communication to the editors of the *Journal of the American Chemistry Society* (received April 25, 1962), Calvin L. Stevens described a novel application of a rearrangement reaction involving α-amino ketones (Stevens et al. 1962). Though this communication did not include the synthesis of any β-keto-arylcyclohexylamines, it laid the synthetic foundation that would later give rise to systematic investigations involving these compounds. What appears to be the first publication to describe a number of β-keto-arylcyclohexylamines and to recognize their clinical potential was a US patent 3,254,124 filed on June 29, 1962 (assigned to Parke-Davis) (Stevens 1962). This patent (granted on May 31, 1966) described the synthesis of a number of important β-keto-arylcyclohexylamines including ketamine, MXM (methoxmetamine), 2-methoxy-2-deschloroketamine (2-MK), DCK, and 2-oxo-PCE. Many of these compounds were also described in more detail in a number of subsequent publications by the Stevens Group focusing on aminoketone rearrangement reactions from the early to mid-1960s (Stevens et al. 1963, 1965a, b, 1966a, b, c; Stevens 1968). Stevens served as a consultant to Parke-Davis during this time and provided these compounds for pharmacological testing.

3.2 Ketamine

In April, 1962, 2-(2-chlorophenyl)-2-(methylamino)cyclohexanone (ketamine) was submitted by Stevens for testing under the test code name CI-369 (McCarthy 1981). During the early 1960s, Parke-Davis and their collaborators conducted a number of pharmacological investigations into ketamine, which would soon be designated

using the clinical code of CI-581 (Chen 1969; McCarthy et al. 1965; Morris and Wallach 2014). The first human subject received ketamine on August 3, 1964 (McCarthy 1981; Domino 2010).

The data from the first human subjects were soon published (Domino et al. 1965). Additional human studies quickly followed, confirming animal studies and establishing CI-581 to be an effective and safe anesthetic and analgesic with an improved tolerability profile over PCP (Corssen and Domino 1966; Chodoff and Stella 1966; McCarthy et al. 1965). This research led to the marketing of ketamine as Ketalar® in 1969 and and its official FDA approval in the USA for use as a general anesthetic in 1970 (Morris and Wallach 2014). Since this time, ketamine has found widespread use internationally as a general anesthetic and is on the World Health Organization's list of essential medicines. In addition to its anesthetic action, ketamine has potent analgesic actions and is successfully used for this purpose (Clements and Nimmo 1981; Kohrs and Durieux 1998). Ketamine also plays an important role in veterinary medicine (Morris and Wallach 2014).

Apart from uses related to traditional medical procedures and recreational or spiritual drug use (Lilly 1996; Jansen 2004), ketamine has also been evaluated for the treatment of drug dependence and neurotic disorders (Krupitsky et al. 2001, 2007). Most recently, ketamine has been increasingly studied for its potential role as an agent in treatment-resistant depression based on initially promising outcomes (e.g., Katalinic et al. 2013; Vutskits 2018; Zanos et al. 2018). In addition to therapeutic uses, ketamine has shown potential in other clinical research applications. For example, administrations of subanesthetic doses of ketamine have been described to mimic certain aspects of psychosis and schizophrenia including positive psychosis symptoms such as hallucinations and altered thoughts, as well as negative symptoms including impairment of cognition, derealization, depersonalization, and withdrawal (e.g., Krystal et al. 1994; Lahti et al. 1995; Malhotra et al. 1996; Vollenweider et al. 1997; Chambers et al. 1999; Newcomer et al. 1999; Pomarol-Clotet et al. 2006; Gouzoulis-Mayfrank et al. 2005; Lodge and Mercier 2015) though important differences exist between drug-induced effects and this spectrum of disorders (Frohlich and Van Horn 2014). For more information, the history of ketamine including its medical and nonmedical use has been described previously (Morris and Wallach 2014; Domino 2010; Lodge and Mercier 2015).

3.2.1 Pharmacokinetics

Ketamine is a weak base with a pK_a of 7.5 (Dayton et al. 1983). The bioavailability of ketamine through different routes of administration has been investigated and was reviewed by Fourcade and Lapidus (2016). Intramuscular injection results in about 93% of bioavailability relative to iv administration. Oral bioavailability of ketamine was reported around 20% due to a substantial first-pass effect, whereas intranasal and sublingual administration have slightly higher bioavailabilities (50% and 30%, respectively) (Fourcade and Lapidus 2016). Ketamine exhibited low but significant affinity for the efflux transporter Pgp as well as a number of other clinically relevant transport proteins including organic cation transporters (Keiser et al. 2018; Amphoux et al. 2006; Massmann et al. 2014).

Modest plasma protein binding has been seen with ketamine including binding to human plasma proteins (up to 47% bound), however differences between studies exist (Dayton et al. 1983). Ketamine is modestly lipophilic (LogP = 2.18) (Hansch et al. 1987) and has been shown to accumulate in rat brain tissue at concentrations 2.3 times higher than the incubation medium in vitro (Cohen and Trevor 1974). The elimination kinetics of ketamine are biphasic. For example, after intravenous application in human subjects, the initial serum half-life (α-elimination phase) was found to be around 11 min resulting from rapid distribution of the drug from plasma to tissue. The β-elimination phase resulting largely from metabolic clearance has been given as 150 min (iv) (Wieber et al. 1975), 186 min (iv) (Clements and Nimmo 1981), and 155 min (im) (Grant et al. 1981).

The metabolism of ketamine has been explored extensively (Mion and Villevieille 2013; Yanagihara et al. 2001; Hijazi and Boulieu 2002; Li et al. 2013b; Clements and Nimmo 1981). Briefly, the major phase I metabolite in humans and rats is norketamine resulting from *N*-demethylation (Mion and Villevieille 2013; Yanagihara et al. 2001; Hijazi and Boulieu 2002; Li et al. 2013b; Clements and Nimmo 1981; Cohen and Trevor 1974). CYP3A4, CYP2C9, and CYP2B6 have been implicated as key enzymes in transformation of ketamine to norketamine (Yanagihara et al. 2001; Hijazi and Boulieu 2002; Li et al. 2013b). The potential for genetic differences in metabolism of ketamine has been considered with a CYP2B6*6 genotype using human liver microsomes, as well as recombinant enzyme systems and human chronic pain patients (Li et al. 2013b, 2015) although a more recent in vivo study in humans failed to confirm this (Rao et al. 2016). Additional phase I metabolites include those from hydroxylation of the cyclohexanone ring of ketamine and norketamine (NK) to form hydroxylated ketamine and norketamine (HNK) metabolites, respectively, that give rise to pairs of diastereomers (Adams et al. 1981; Rao et al. 2016). The formation of 5,6-dehydro-NK (DHNK) has also been reported (Rao et al. 2016). In one study, DHNK formation has been attributed to nonenzymatic (artificial) degradation of the corresponding HNK species due to analysis by gas chromatography mass spectrometry (GC-MS) (Adams et al. 1981). In a study evaluating a 40 min ketamine infusion (0.5 mg/kg, iv), higher plasma concentrations of DHNK, (2*S*,6*S*;2*R*,6*R*)-HNK, (2*S*,6*R*;2*R*,6*S*)-HNK, and (2*S*,5*S*;2*R*,5*R*)-HNK were detected patients with bipolar depression (BD) compared to patients with major depressive disorder (MDD) who had higher concentrations of (2*S*,6*S*;2*R*,6*R*)-HNK. Notably, MDD patients were required to be medication free for at least 2 weeks (5 weeks for fluoxetine) prior to ketamine infusion, whereas BD patients took either lithium or valproate within a specified range (Zarate et al. 2012). Phase II metabolism of ketamine in humans has been observed, most notably in the form of HNK-glucuronides (Turfus et al. 2009; Moaddel et al. 2010). It should also be noted that differences in metabolism of (*R*)- and (*S*)-ketamine have been observed (Kharasch and Labroo 1992). Finally, tolerance to repeated ketamine doses in rats has been reported to involve increased hepatic metabolism through induction (Livingston and Waterman 1978; Marietta et al. 1976). Efforts have been taken to create analogs of ketamine with altered pharmacokinetics. For example, the evaluation of five aliphatic norketamine esters in rabbits (venous cannulation of marginal

ear vein) revealed that this structural modification gave rise to rapid metabolism via hydrolysis to the corresponding carboxylic acid derivatives, which were inactive in vivo in the models tested (Harvey et al. 2015).

3.2.2 Pharmacodynamic Effects In Vitro

Detailed reviews on the pharmacodynamics of ketamine are available (e.g., Mion and Villevieille 2013; Lodge and Mercier 2015; Fourcade and Lapidus 2016; Laher et al. 2015). Ketamine has moderate affinity for the PCP binding site of NMDAR (Table 2) (Roth et al. 2013; Colestock et al. 2018; more in vitro data reviewed in Hondebrink et al. 2018). Ketamine has been shown to block NMDARs in numerous in vitro and ex vivo models (Anis et al. 1983; Hirota and Lambert 1996; Kang et al. 2017). This blockade has been shown to be use- (uncompetitive) and voltage-dependent (MacDonald et al. 1987; Davies et al. 1988; Kang et al. 2017). Differences in NMDAR affinity and NMDAR channel blocker potency are seen between enantiomers with (*S*)-ketamine being about 2–5× more potent than (*R*)-ketamine (Hirota and Lambert 1996; Zeilhofer et al. 1992; Ebert et al. 1997; Oye et al. 1991, 1992). The major metabolite, norketamine, is also a modest affinity NMDAR antagonist ($K_i = 3{,}600$ nM, [^{3}H]MK-801 in rat brain) although with lesser potency than ketamine (Ebert et al. 1997). The metabolite (2*R*,6*R*)-HNK did not inhibit currents evoked by NMDA application to rat stratum radiatum interneurons in hippocampal slices at >10 μM but has been shown to have activity as a modulator of AMPA (increased frequency and amplitude of AMPA receptor-mediated excitatory postsynaptic potentials from rat CA1 stratum radiatum interneurons), at 10 μM concentration (Zanos et al. 2016). Recently, 50 μM concentrations of HNK were found to block NMDAR currents in cultured hippocampal neurons (C57BL/6 mice, postnatal day 1–3) (Suzuki et al. 2017). Ketamine has been shown to impair LTP induction in the brains of rodents, likely through NMDAR antagonism, using several different experimental designs (e.g., Zhang and Levy 1992; Ribeiro et al. 2014).

Recently, Can et al. (2016) found no significant inhibition of reuptake at human SERT, DAT, or NET by ketamine or several metabolites tested ($IC_{50} > 10{,}000$ nM) in transfected HEK293 cells. Similar results were observed when looking at receptor binding to these human monoamine transporters in transfected HEK293 cells (Roth et al. 2013, 2018). However, at higher concentrations ketamine has been reported to bind to monoamine transporters (expressed in HEK293 cells) though with fairly weak potency with K_i values of 66.8 μM (human NET), 62.9 μM (rat DAT), and 161.7 μM (rat SERT) (Nishimura et al. 1998). A follow-up study found stereospecific effects at DAT with (*S*)-ketamine showing ~eightfold greater affinity than (*R*)-ketamine (Nishimura and Sato 1999). Ketamine was also found to inhibit [^{3}H]5-HT, [^{3}H]DA, and [^{3}H]NA uptake in rat synaptosomal fractions (cerebral cortex) with highest effects observed for serotonin transport (Azzaro and Smith 1977), which was consistent with work published later by Smith et al. (1981) using synaptosomal preparations (Sprague-Dawley, cerebral cortex). Stereospecific effects of ketamine have been seen on both stimulated efflux and reuptake for DA, NE, and 5-HT in rat brain slices (Tso et al. 2004).

Table 2 Receptor binding affinities of β-keto-arylcyclohexylamines at key CNS receptor sites

Compound	NMDAR	NET	DAT	SERT
Ketamine	$K_i = 323.9$ nM Colestock et al. (2018) $K_i = 659$ nM Roth et al. (2013) $IC_{50} = 800$ nM Quirion et al. (1981) $K_i = 607$ nM Tam and Zhang (1988) $K_i = 530$ nM Ebert et al. (1997)	$IC_{50} > 10{,}000$ nM Roth et al. (2013) $K_i = 66.8$ μM Nishimura et al. (1998)	$IC_{50} > 10{,}000$ nM Roth et al. (2018) $K_i = 62.9$ μM Nishimura et al. (1998)	$IC_{50} > 10{,}000$ nM Roth et al. (2013) $K_i = 161.17$ μM Nishimura et al. (1998)
(*S*)-(+)-Ketamine	$K_i = 900$ nM Oye et al. (1991) $K_i = 1{,}200$ nM Oye et al. (1992) $K_i = 300$ nM Ebert et al. (1997)	$K_i = 64.8$ μM Nishimura and Sato (1999)	$K_i = 46.9$ μM Nishimura and Sato (1999)	$K_i = 156$ μM Nishimura and Sato (1999)
(*R*)-(−)-Ketamine	$K_i = 2{,}500$ nM Oye et al. (1991) $K_i = 5{,}000$ nM Oye et al. (1992) $K_i = 1{,}400$ nM Ebert et al. (1997)	$K_i = 68.9$ μM Nishimura and Sato (1999)	$K_i = 390$ μM Nishimura and Sato (1999)	$K_i = 148$ μM Nishimura and Sato (1999)
MXE	$K_i = 259$ nM Roth et al. (2013)	$IC_{50} => 10{,}000$ nM Roth et al. (2013)	$IC_{50} > 10{,}000$ nM Roth et al. (2018)	$K_i = 481$ nM Roth et al. (2013)

Radioligands and tissue preparations used for NMDAR binding: [^{3}H]MK-801 in rat brain (Roth et al. 2013). Oye et al. (1991): [^{3}H]TCP (guinea pig brain). Oye et al. (1992): [^{3}H]MK-801 (guinea pig brain); Tam and Zhang (1988): [^{3}H]MK-801 (human brain); Ebert et al. (1997): [^{3}H]MK-801 (in rat cortex, hippocampus, and striatum). Radioligands and tissue preparations used for DAT, NET, and SERT: Roth et al. (2013, 2018): *N*-methyl-[^{3}H]nisoxetine (NET), [^{3}H]WIN35,428 (DAT), [^{3}H]citalopram (SERT) in HEK293 cells transfected with human transporters. Nishimura et al. (1998) and Nishimura and Sato (1999): ([^{3}H]5-HT, [^{3}H] NE, [^{3}H]DA) in HEK293 cells transfected with human NET, rat DAT, and rat SERT. A summary of in vitro data related to ketamine has been provided by Hondebrink et al. (2018)

It should be noted it is unlikely that monoamine reuptake inhibition contributes much to the pharmacology of ketamine in vivo even at high doses due to the high concentrations needed for such effects. Ketamine can however indirectly alter monoamine turnover (Kokkinou et al. 2018; Laher et al. 2015), and this may occur at physiologically relevant concentrations.

A receptor binding study uncovered that ketamine lacked notable affinity ($IC_{50} > 10{,}000$ nM) for a number of important CNS receptors including receptors for 5-HT, dopamine, norepinephrine, histamine, as well as opioid (MOR, KOR, and DOR) and sigma-1 and sigma-2 receptors (Roth et al. 2013, 2018). At concentrations greater than 10,000 nM, ketamine has been found to interact with a number of receptors. For example, both (*R*)- and (*S*)-ketamine were found to have low affinity toward the μ-opioid receptor (MOR) (28 μM and 11 μM, respectively) and low affinities at DOR and KOR receptors using guinea pig brain homogenate (Hustveit et al. 1995), and this was consistent with results reported elsewhere (Hirota et al. 1999). Likewise, low affinities (>10,000 nM) have been reported at sigma and muscarinic receptors with both enantiomers (guinea pig brain homogenate) (Hustveit et al. 1995; Hirota and Lambert 1996). A 500 nM affinity (K_i) and agonist activity was reported for D_2 receptors in rat brain (Kapur and Seeman 2002). Interestingly, ketamine and PCP were reported in a later study by this group to have even higher affinity (55 nM and 2.7 nM, respectively) and functional activity at the high-affinity state of the D_2 receptor (Seeman et al. 2005). These results however have been considered controversial (Svenningsson et al. 2004), and other studies were inconsistent with these findings (Aalto et al. 2002; Jordan et al. 2006; Can et al. 2016; Roth et al. 2018). Low affinity ($K_i = 15$ μM) and agonist activity was also reported at 5-HT_2 receptors in rat brain (Kapur and Seeman 2002).

The understanding of ketamine pharmacology continues to evolve. One interesting avenue to pursue involves the interaction of ketamine with various ion channels. Although a detailed overview is outside the scope of this chapter, the interaction of ketamine with various ion channels has been reviewed. In summary, ketamine has been found to inhibit a range of channels including those of cations K^+, Na^+, and Ca^{2+} as well as hyperpolarization-activated cyclic nucleotide-gated (HCN) channels (reviewed by Laher et al. 2015). An EC_{50} of 8–16 μM for HCN1-HCN2 channel inhibition has been seen with ketamine using electrophysiological recordings in HEK293 cells transfected with mouse HCN channel constructs. In addition, (*S*)-ketamine was two times more potent than the racemate at inhibiting HCN1-HCN2 channels. Fascinatingly, HCN1 antagonism has been implicated in some of the hypnotic effects of ketamine (see Sect. 3.2.3 below) (Chen et al. 2009).

3.2.3 Effects In Vivo

The effects of ketamine in vivo have been extensively described elsewhere (e.g., Kreuscher 1969; Domino 2018). As an illustration of its potential for positive reinforcement, ketamine has been shown to be self-administered in rhesus monkeys (Moreton et al. 1977) and rats (De Luca and Badiani 2011). Similar to other dissociatives, ketamine dose-dependently disrupts PPI in rats (male Wistar and Sprague-Dawley) (de Bruin et al. 1999; Cilia et al. 2007; Halberstadt et al. 2016).

The effect is stereospecific with (*S*)-ketamine having an ED_{50} of 2.86 mg/kg and (*R*)-ketamine an ED_{50} of 6.33 mg/kg for PPI disruption (Halberstadt et al. 2016). Interestingly, ketamine increased PPI in healthy human male volunteers although this might have been related to the relatively low doses used and higher-dose studies in humans are warranted to explore this further (Abel et al. 2003; Heekeren et al. 2007). Ketamine increases dopamine levels in certain areas of the animal brain in vivo, which might be relevant when considering abuse liability (Kokkinou et al. 2018). In addition the HCN1 receptor has been implicated in the hypnotic effects of ketamine as HCN1 knockout mice show reduced sensitivity to the hypnotic effects of ketamine (Chen et al. 2009).

Ketamine has shown activity in a number of experimental models known to be predictive of antidepressant activities in humans including the forced swim test and tail suspension tests in rodents, with the (*R*)-isomer typically showing more sustained effects (Garcia et al. 2008; Koike and Chaki 2014; Zhang et al. 2014; Salat et al. 2015; Niciu et al. 2014). Ketamine and (*S*)-ketamine have also been shown to have potent analgesic effects in several experimental models in animals including rats but also humans (Clements and Nimmo 1981; Koinig et al. 2000; Holtman et al. 2008).

Ketamine has shown anticonvulsant effects as defined as prevention of the tonic hindlimb extensor reflex in the maximal electroshock seizure test (MES) in mice (ip, $ED_{50} = 43.7$ mg/kg, Parsons et al. (1995); sc, $ED_{50} = 15.1$ mg/kg, Leander et al. (1988)). Ketamine also caused impairment in the rotarod (ip, $ED_{50} = 67.4$ mg/kg), traction reflex ($ED_{50} = 53.8$ mg/kg) (Parsons et al. 1995), and horizontal screen test (sc, $ED_{50} = 23$ mg/kg) (Leander et al. 1988). Potency of ketamine in these models is significantly reduced relative to PCP (Wallach and Brandt 2018). Both MES test and rotarod potency have been found to correlate with NMDAR PCP site affinities (Wallach 2014).

Tolerance to the behavioral effects has been observed with repeated ketamine administration in animals including humans (Cumming 1976; Marietta et al. 1976; Livingston and Waterman 1978; MacLennan 1982). Interestingly, a pharmacokinetic component to tolerance, through self-induction of hepatic metabolism, may be at least partially involved as repeated ketamine treatment led to increased metabolic rates in rats (Marietta et al. 1976; Lin et al. 2015).

3.2.4 Clinical Toxicology

Common symptoms of ketamine intoxication include hallucinations, altered mental status, tachycardia, hypertension, mydriasis, and nystagmus (Weiner et al. 2000; Ng et al. 2010). A controlled study of subanesthetic doses of ketamine revealed dose-dependent increases in blood pressure (Krystal et al. 1994). Elevation in plasma cortisol and prolactin were also reported (Krystal et al. 1994). Though ketamine has a wide safety margin, reports of fatal overdoses have been described. These generally involved behavioral effects and included motor vehicle accidents, drowning, and other accidents (Morgan and Curran 2012). However, fatalities from polydrug use as well as cases involving only ketamine including a ketamine-related homicide have been described (Licata et al. 1994; Moore et al. 1997; Lalonde and Wallage

2004; Morgan and Curran 2012). Postmortem toxicology including blood levels (1.8–27.4 mg/L and 0.6-1.8 mg/L in femoral blood) in six reported fatalities has been reviewed by Watterson (2015).

Ketamine dependence and discontinuation symptoms have been described in a number of cases (e.g., Lim 2003; Critchlow 2006; Pal et al. 2002; Hurt and Ritchie 1994). Discontinuation effects described in a 25-year-old male user of ketamine (6-year history) included anxiety, shaking, sweating, palpitations, low mood, drowsiness, and loss of appetite. The time course was described and it was reported that ethanol and diazepam consumption decreased some of the symptoms experienced (Critchlow 2006).

Ketamine has shown toxicity in a number of different experimental models; however the relevance to humans remains poorly understood in most cases (e.g., Li et al. 2013a; Ho and Dargan 2017). On the other hand, urotoxicity and cystitis have been extensively documented among heavy recreational ketamine users (Chu et al. 2007; Shahani et al. 2007; Shahani and Stewart 2008; Tsai et al. 2009; Morgan and Curran 2012). While most cases reported involve nonmedical use and appear to be positively associated with dose and frequency of use, ketamine-induced cystitis has also been documented with medical use for example in patients using ketamine for pain (Storr and Quibell 2009). Ketamine-induced cystitis has been investigated in animal and in vitro models although the pathogenesis remains incompletely understood (Tan et al. 2011; Tang et al. 2015). The toxicology of ketamine including clinical as well as in vitro and in vivo studies in nonhuman animals has been reviewed (e.g., Li et al. 2013a; Ho and Dargan 2017).

3.3 Methoxetamine

Methoxetamine (MXE) (Fig. 2) is the β-keto-derivative of the arylcyclohexylamine research chemical 3-MeO-PCE (Wallach and Brandt 2018). The fascinating history of MXE and how it was developed has been described elsewhere (Morris 2011; Morris and Wallach 2014). Briefly, MXE was designed and explored by a UK chemist attempting to develop an improved version of ketamine to treat his phantom limb pain. The main intentions were to increase potency and duration of action of the treatment and in the process to reduce the risk of bladder toxicity seen with ketamine (Morris 2011; Morris and Wallach 2014). This perceived reduction in bladder toxicity has been reported as a motivation for use among some users (Winstock et al. 2016) although the validity of this theory remains to be established. MXE became available for purchase as a research chemical in 2010 and was notified to the EMCDDA shortly afterward in November of the same year (EMCDDA–Europol 2011). At the present time MXE remains a popular research chemical even though it has been placed under international control.

MXE induces mild dissociative effects starting around 5–10 mg and is active via oral and parenteral routes although potency differs with parenteral routes being generally more potent. Reports on ingestion of higher doses are common with strong dissociative effects and hallucinations generally requiring 30–60 mg. MXE appears

to be around two to threefold more potent than ketamine in human subjects, which is consistent with NMDAR receptor binding affinities and results from animal studies (Horsley et al. 2016; Roth et al. 2013; Halberstadt et al. 2016). Durations of effects depend on the route of administration but are consistently of longer duration than ketamine: insufflation (2.4–4 h), oral (3–5 h), and im (2–3 h). Subjective effects that have been described include euphoria, a sense of calm and serenity, distortion or loss of sensory perception, severe dissociation, depersonalization, and loss of consciousness similar to effects of classical hallucinogens, like LSD and psilocybin, and ketamine (Kjellgren and Jonsson 2013). Since the emergence of MXE, extensive research data have been accumulated within the last few years, and a complete review is out of scope of this chapter although representative information and key studies have been included. Review articles on MXE have been published (e.g., Corazza et al. 2013; WHO 2014; Zawilska 2014; Zanda et al. 2016). It is worth noting that bromo-MXE (Fig. 2) was detected in August 2013 in a sample containing MXE in Europe (EMCDDA–Europol 2014), which indicated that it might have been produced by overbromination during MXE synthesis. No reports on its use or availability could be identified online.

3.3.1 Pharmacokinetics

Following subcutaneous administration of MXE (male Wistar rats, 10 mg/kg), the analysis of brain, liver, and lung tissue at different time points revealed that that highest MXE concentrations in all three tissues were observed within the first hour. Within the first hour, highest concentrations of the *N*-demethyl metabolite nor-MXE were detected in lung tissue, whereas *O*-demethyl-MXE was highest in the liver (Hajkova et al. 2016). An extension of this work confirmed the MXE brain-to-serum ratio to be between 2.06 and 2.93 during the time course of the study. In addition, a longer duration of action, relative to ketamine, was reported, and this was consistent with the time course of detected serum and brain concentrations (Horsley et al. 2016).

A number of studies have investigated metabolism of MXE using in vitro and in vivo methods in rat and humans. Results have been for the most part consistent with ketamine biotransformation and which included *N*- and *O*-dealkylation, hydroxylation of the aryl and aliphatic rings, and detections of dihydro-MXE, dihydronor-MXE, and dihydro-*O*-demethyl-MXE as major phase I metabolites (Meyer et al. 2013a; Menzies et al. 2014; Hajkova et al. 2016; Horsley et al. 2016). In vitro enzyme studies also revealed that CYP2B6 and CYP3A4 isoforms were involved in *N*-deethylation of MXE, whereas CYP2B6 and CYP2C19 were implicated in *O*-demethylation. A comparatively minor formation of the hydroxy-aryl-MXE metabolite was formed during incubation with CYP2B6. Another interesting observation made during the derivatization of metabolite samples for analysis by gas chromatography mass spectrometry was the formation of a cyclized artifact (Meyer et al. 2013a). It should be noted that CYP3A4 and CYP2B6 also play an important role in the metabolism (via *N*-demethylation) of ketamine to its major phase I metabolite norketamine (Yanagihara et al. 2001; Hijazi and Boulieu 2002; Li et al. 2013b). Detected phase II metabolites of MXE include sulfate and

glucuronide metabolites of phase I metabolites (Menzies et al. 2014; Meyer et al. 2013a; Horsley et al. 2016). Nor-MXE (and in one case dihydro-MXE) were found to be the most abundant metabolites in human urine samples (Meyer et al. 2013a; Menzies et al. 2014). In rat urine (male Wistar, sc), the most abundant metabolite (~15%) was *O*-demethyl-MXE followed by nor-MXE (~4%) and dihydro-*O*-demethyl-MXE (~3%) following a subcutaneous injection of 40 mg/kg. The majority of MXE (~75%) was excreted unchanged in urine (Horsley et al. 2016).

3.3.2 Pharmacodynamic Effects In Vitro

MXE showed moderate affinity at the PCP binding site of NMDAR ($K_i = 259$ nM), which was about twofold greater than ketamine ($K_i = 659$ nM) (Roth et al. 2013). This increased affinity is consistent with anecdotal reports of two to threefold greater potency of MXE relative to ketamine in humans and animal studies (Halberstadt et al. 2016). 3-MeO-PCE ($K_i = 61$ nM) had ~4.2-fold higher NMDAR affinity than MXE (Roth et al. 2013) suggesting that the β-keto function decreases NMDAR affinity and potency. Consistent with this, 3-MeO-PCE is about 2-3 fold more potent than MXE via nasal insufflation (personal communication). More structure-activity research is needed to better define the effect of the β-keto substitution on these compounds.

MXE also showed affinity for human SERT (481 nM) but lacked significant affinities ($IC_{50} > 10{,}000$ nM) at human NET and DAT as well as sigma-1 and sigma-2 receptors (Roth et al. 2013). Consistent with the receptor binding studies, MXE was found to block uptake of monoamines at human DAT ($IC_{50} = 33$ μM), NET ($IC_{50} = 20$ μM) and most strongly for SERT ($IC_{50} = 2{,}400$ nM and 2,000 nM) in transfected HEK293 cells (Zwartsen et al. 2017; Hondebrink et al. 2017). MXE inhibited neuronal (electrical) activity ($IC_{50} = 500$ nM) (predominantly characterized as displaying excitatory glutamatergic neurons, inhibitory GABAergic neurons, and astrocytes) using a multi-well microelectrode array. Under these conditions, neuronal activity and modulation represents a measurable integrated output, thus, detailed information about mechanistic features is unavailable. The inhibition of neuronal activity has also been observed with other test substances such as GABA and diazepam (Hondebrink et al. 2016). In a follow-up study, MXE as well as ketamine were evaluated in rat primary cortical cells ($IC_{50} = 500$ and 1,200 nM, respectively), human SH-SY5Y cells, human induced pluripotent stem cell (hiPSC)-derived iCell® neurons, DopaNeurons and astrocyte co-cultures. A number of conditions were investigated, but, in summary, MXE inhibited neuronal activity in rat cortical cultures and iPSC-derived neurons, inhibited voltage-gated Ca^{2+} channels in SH-SY5 cells, and increased glutamate-evoked increase in intracellular Ca^{2+} in rat cortical cultures (Hondebrink et al. 2017).

3.3.3 Effects In Vivo

The available data currently suggest that MXE displays rewarding and reinforcing effects and thus potential abuse liability especially in predisposed individuals. In adult male Sprague-Dawley rats, electrophysiological investigations uncovered that MXE dose dependently stimulated firing and burst rate of ventral tegmental area

dopamine neurons projecting to the nucleus accumbens (NAc) shell after injection of cumulative doses of MXE (0.031–0.5 mg/kg, iv). Correspondingly, and consistent with observations reported with ketamine and PCP, MXE increased extracellular dopamine levels in the NAc shell (0.125, 0.25 and 0.5 mg/kg, iv) using microdialysis studies in freely moving male Sprague-Dawley rats. MXE was also found to substitute for ketamine in a self-administration paradigm in male Sprague-Dawley rats (Mutti et al. 2016). Furthermore, MXE was reported to produce conditioned place preference (2.5 and 5 mg/kg) and to be self-administered in male Sprague-Dawley rats (0.25, 0.5, 1.0 mg/kg, iv infusion). The self-administration was reported to be modest relative to that seen with ketamine (0.5 mg/kg) (Botanas et al. 2015). MXE generalized to ketamine in discriminative stimulus model in male Sprague-Dawley rats (Chiamulera et al. 2016). Interestingly, the highest dose of LSD (0.3 mg/kg) tested also showed (77%) generalization to ketamine (all lower doses tested also showed some generalization). In male Sprague-Dawley rats, MXE (ED_{50} = 0.25 mg/kg) substituted for 3 mg/kg PCP (ED_{50} = 1.25 mg/kg) in a discriminative stimulus test. However substitution was not seen in all animals tested and there was also a reduction in response rates. In addition, MXE dose-dependently reduced PCP withdrawal symptoms and was self-administered (albeit to a lesser extent than PCP) in these rats. MXE also elicited dose-dependent (10–56 mg/kg) hypothermic effects on male NIH Swiss mice (Berquist et al. 2017).

Interestingly, increased locomotor activity in rodents has been observed under some experimental conditions (Halberstadt et al. 2016 (10 mg/kg, sc); Horsley et al. 2016 (5 and 10 mg/kg, sc)) but not in others (Berquist et al. 2017, 1–30 mg/kg, ip; Botanas et al. 2015 (1.25–5 mg/kg, ip)), which, in part, might have been related to dose, species, and strain differences. Higher doses (40 mg/kg) reportedly caused sedation and hypolocomotion in male Wistar rats (Horsley et al. 2016). Another recent study in male Sprague-Dawley rats evaluated a number of behavioral effects of MXE following ip administration. MXE affected spontaneous motor activity dose and time dependently where lower doses (0.5 mg/kg) were associated with hypermotility, whereas higher doses (2.5–5 mg/kg) were generally associated with hypomotility at various time points after administration. In addition to these effects, 5 mg/kg MXE induced transient analgesia in the tail-flick and hot-plate test and increased swimming activity in the forced swim test (Zanda et al. 2017). As stated previously, the forced swim test is a model used for assessing drugs for potential antidepressant activity in humans. MXE (2.5, 5, or 10 mg/kg, ip) was claimed to have "rapid and sustained antidepressant effects" in several models predictive of antidepressant activity in humans including the forced swim test, tail suspension test, and sucrose preference test in male ICR mice. These effects were suggested to be mediated through glutamatergic and serotoninergic mechanisms based on RT-PCR and pharmacological antagonism experiments (Botanas et al. 2017).

Consistent with PCP, ketamine, and other NMDAR antagonists, MXE (sc) caused dose-dependent disruption of PPI (ED_{50} = 1.89 mg/kg) in male Sprague-Dawley and Wistar rats (Halberstadt et al. 2016; Horsley et al. 2016). The effect on PPI was more potent than those recorded for (*S*)-ketamine

(ED_{50} = 2.86 mg/kg) and (*R*)-ketamine (ED_{50} = 6.33 mg/kg) but less than PCP (ED_{50} = 0.88 mg/kg) consistent with NMDAR affinities (Halberstadt et al. 2016).

Histological investigations following daily MXE administration (30 mg/kg, ip) for a period of 3 months were shown to induce statistically significant bladder and kidney toxicity in male ICR mice (Dargan et al. 2014). Comparable effects have been described with ketamine at (30 mg/kg, ip) (Yeung et al. 2009; Tan et al. 2011). Furthermore, chronic treatment (30 mg/kg daily for 4 or 12 weeks) caused inflammation and dysfunction in female Sprague-Dawley rat bladder and cytotoxic and pro-inflammatory effects in human urothelial cells (SV-HUC-1) similar to what has been shown with ketamine (Wang et al. 2017).

3.3.4 Clinical Toxicology

Case reports describing a range of clinical features associated with MXE intoxication and adverse effects have been abundantly published, and a complete overview is outside the scope of this chapter. From this perspective, a number of representative examples from the literature will be presented, and further information may be obtained from more extensive reviews (e.g., EMCDDA 2014; WHO 2014; Zawilska 2014; Zanda et al. 2016). Many factors influence drug use, but it should be noted that examples exist in the case report literature where MXE use was motivated by attempts to self-medicate for various reasons, such as reduction of high-dose codeine intoxication (Sein Anand et al. 2012), chronic foot pain (Maskell et al. 2016), and post-traumatic stress disorder (Striebel et al. 2017).

What appeared to be among the first reports on the acute toxicity of MXE involved a 32-year-old male who was described as initially agitated and in a dissociative state following self-reported intramuscular administration. Clinical signs included tachycardia (105 bpm), hypertension (140/95), mydriasis with pupils reactive, and bilateral rotatory nystagmus. Respiration rate (16), blood glucose (122 mg/dL), and oxygen saturation (98%) were normal. The patient returned to "baseline mental status" within 8 h. Although a powdered sample was shown to consist of MXE, analytical confirmation from biofluids was unavailable (Ward et al. 2011).

Ketamine-like effects were reported in a 19-year-old male with a history of drug use and psychiatric disorders who was receiving treatment with bupropion, aripiprazole, and chlorprothixene. Following an iv injection of an unknown amount of MXE, the patient was admitted to the hospital with extreme agitation, ataxia, and a semistuporous state. Consistent with other reports, the clinical features described included tachycardia, hypertension, confusion, agitation, stupor, ataxia, mydriasis, and nystagmus (Hofer et al. 2012).

Three cases (males aged 42, 29, and 28 years) involving MXE intoxication were associated with ketamine-type dissociative/catatonic effects but also acute sympathomimetic toxicity. Case 1 involved a 42-year-old male found "collapsed" in the street. He was noted to be drowsy (Glasgow Coma Score 6/15), tachycardic (135 bpm), hypertensive (187/83 mmHg), and pyrexial (38.2°C). The serum concentration of MXE detected was 120 ng/mL. The NPS stimulant and sympathomimetic drug 5/6-APB (isomer not determined) was also detected but not quantified

and the patient reported ingesting 3 pints of beer. Case 2 involved a 29-year-old male found "catatonic" by his mother. He had tremor, visual hallucinations, confusion, and mydriasis. At the ER he was found to be confused, tachycardic (121 bpm), and hypertensive (201/104 mmHg). The MXE serum concentration was 90 ng/mL. Diphenhydramine and venlafaxine were also detected. The third case involved a 28-year-old male who had collapsed in the bathroom of a nightclub. He developed worsening agitation and aggression en route to the emergency department. He was tachycardic (113 bpm) and hypertensive (198/78 mmHg) and had mydriasis. The serum concentration of MXE detected was 200 ng/mL (Wood et al. 2012). Subsequently, three further cases (males aged 19, 18, and 18 years) have been described that included clinical features of severe truncal ataxia, nystagmus, incoordination, and reduced conscious level several hours after nasal insufflation. Features of cerebellar toxicity persisted 3–4 days in one case (19-year-old male). Slurred speech, incoordination, and cerebellar ataxia were also noted in addition to sympathomimetic features (Shields et al. 2012).

What appears to be one of the earliest accidental fatal intoxications involving MXE was reported in 2013 in which the MXE concentration found in femoral blood was 8,600 ng/g. Therapeutic concentrations of venlafaxine (300 ng/g) and *O*-demethylvenlafaxine (400 ng/g) were detected in addition to tetrahydrocannabinol (1 ng/g). Three synthetic cannabinoid receptor agonists (AM-694, AM-2201, and JWH-018) were also detected (<1 ng/g). These other substances may have contributed to the fatal outcome (Wikstrom et al. 2013). An estimated blood concentration of 5,800 ng/mL (urine: 85,000 ng/mL) MXE has been reported in another case of fatal intoxication in a 29-year-old male (Adamowicz and Zuba 2015).

Chronic recreational ketamine use has been associated with bladder toxicity (e.g., ulcerative cystitis) (Morgan and Curran 2012), and further studies are needed to assess the extent to which this might also apply to MXE. As stated previously, nonhuman animal and in vitro studies suggest it to be a possibility especially with higher doses and frequent use (Dargan et al. 2014; Wang et al. 2017). Furthermore, a survey carried out in 2012 including respondents who reported having ever used ketamine and MXE in the past 12 months revealed that 23% reported experiencing urinary symptoms (e.g., frequent urination, or pain in lower abdomen, etc.) although previous ketamine use could not be ruled out as a causative or contributing factor (Lawn et al. 2016).

3.4 Deschloroketamine (DCK)

Since 2015, a drug testing service coordinated by the drug information center Erowid disseminated information about the detection of deschloroketamine (2-oxo-PCMe, DCK) in powdered samples originating from the USA, China, and Europe. In addition, some of the samples were mislabeled (EcstasyData.org 2018). The detection of DCK has also been reported in 2015 in Barcelona (Spain) (Energycontrol 2015). Two samples recently sold as 2-oxo-PCMe were

subsequently found to be 2-oxo-PCE based on analysis by GC-MS (Wallach and Morris unpublished). DCK is available from online vendors (Van Hout and Hearne 2017). A patent describing the synthesis of DCK was filed in 1962 (Stevens 1962), followed by various publications afterward (Stevens et al. 1963, 1966a, b; Preiss and Tatar 1995; Brunner et al. 2003) including descriptions published in the public domain (Anonymous 2007). The synthetic preparation of DCK has also been featured on a TV program (Viceland 2017). DCK was first reported to the EMCDDA in March 2015 (EMCDDA–Europol 2016), and analytical data have been published (Frison et al. 2016; Maixner et al. 2017) including X-ray powder diffraction analysis on the (*S*)-enantiomer (Maixner et al. 2017). Some analytical information is also available in the public domain (Hungarian Institute for Forensic Science 2016). DCK is currently a fairly popular research chemical with a great deal of discussion on online forums touting its desirable activity profile. DCK was found to be a potent dissociative agent able to induce ethanol-like dissociative effects beginning with doses as low as 4 mg (nasal insufflation of the HCl salt) although higher doses induce more potent dissociative effects (personal communication). Users on Internet forums report a range of doses and routes of administration. The use of DCK for the treatment of bacterial, fungal, viral, or protozoal infections and for immunomodulation has been described. Claimed clinical examples included treatment of cerebral toxoplasmosis, cytomegalovirus infection, conjunctivitis, herpes, and infections associated with HIV (Preiss and Tatar 1995).

3.5 Deschloro-*N*-Ethyl-Norketamine (2-Oxo-PCE)

2-oxo-PCE was apparently the first β-keto-arylcyclohexylamine evaluated by Parke-Davis from the lab of Calvin Stevens. Based on the positive results observed with 2-oxo-PCE, Stevens and his group synthesized and submitted a number of related compounds to Parke-Davis for further testing which led to the identification of ketamine (McCarthy 1981). The synthesis of 2-oxo-PCE was included in the same patent used for the disclosure of the DCK procedure (Stevens 1962), followed by additional examples (Stevens et al. 1966a, 1972). Samples of 2-oxo-PCE have been identified in powdered samples including examples where they were sold as DCK (EcstasyData.org 2018). 2-oxo-PCE induced dissociative effects and strong analgesic effects at 4 mg (nasal insufflation of HCl salt) with an ~3 h duration. Higher doses (17 mg via nasal insufflation) were reported to induce strong dissociatives effects that were said to be "equal to 80 mg of ketamine" (personal communication). The first detection of 2-oxo-PCE has been reported to the EMCDDA in August 2016 (EMCDDA–Europol 2017). Some analytical information is also available in the public domain (Slovenian National Forensic Laboratory 2016). The related *N*-propyl analog 2-oxo-PCPr is a potent dissociative compound capable of inducing ethanol-like effects beginning around 3 mg (nasal insufflation of the HCl salt) (personal communication); however it does not appear to have been sold as a research chemical to date.

3.6 Other β-Keto-Arylcyclohexylamines

A number of additional β-keto-arylcyclohexylamines continue to be offered for sale on the NPS market (Fig. 2). Some reports of dissociative effects with these compounds can be found on numerous online discussion forms (e.g., reddit.com, bluelight.ru, drugs-forum.com). As described in the previous cases, the origin of many of these compounds can be traced back to the scientific literature although a few appear to be novel creations (FXE). The available data on these compounds are currently limited but some are commercially available as reference material.

3.6.1 *N*-Ethylnorketamine (NEK)

The structure of NEK was captured in a patent published by Stevens (e.g., 1962). Some information on the effects of NEK emerged in 2010 followed by increasing discussions on user forums when it emerged into the public space in 2012 (Morris and Wallach 2014). The first detection of NEK was reported to the EMCDDA in September 2012 (EMCDDA–Europol 2013). A published report exists about its detection from samples obtained from uncompleted postal deliveries to Northern Ireland (Jones et al. 2016).

3.6.2 2-Methoxy-2-Deschloroketamine (2-MK)

The synthesis of 2-MK (dinoket) was described in a patent published by Stevens (e.g., 1962) as well as in research article format (Stevens et al. 1966c). Similar to NEK, the interest in 2-MK as a research chemical originated in 2010 when first claims about its psychoactive properties became openly available. However, reports indicated that its effects in users might have been considered disappointing when it became available as a research chemical in 2012 in part due to low potency (Morris and Wallach 2014). 2-MK was first reported to the EMCDDA in August 2012 (EMCDDA–Europol 2013). Its detection has since been reported in Sweden (Backberg et al. 2018), and a conversion of racemic 2-MK into the corresponding diastereomers with trifluoroacetyl-L-prolyl chloride followed by GC-MS analysis for analytical purposes has been published (Weiß et al. 2015).

3.6.3 Methoxmetamine (MXM)

MXM has been described as an active dissociative with reduced potency and shorter duration than MXE with 50–100 mg doses described as active (oral and parenteral) by users on online discussion forms although reports of higher doses exist. This is consistent with the difference in potency and NMDAR binding affinity between 3-MeO-PCMe and 3-MeO-PCE (Wallach and Brandt 2018). Reports of MXM as a research chemical started to appear online in 2014 (Anonymous 2014). A test purchase from an online research chemical vendor was tentatively confirmed by GC-MS and nuclear magnetic resonance spectroscopy (NMR) (Wallach unpublished). The identification of a MXM sample seized in Japan (termed MMXE) and its analytical characterization have been described (Kaizaki-Mitsumoto et al. 2016).

3.6.4 2-Fluoro-2-Deschloroketamine (2-FDCK)

The synthesis of 2-FDCK has been reported (Wang and Li 1987; Moghimi et al. 2014), and discussions about 2-FDCK on online drug discussion forms started to surface in 2015 (e.g., Anonymous 2015a, 2017). 2-FDCK was offered for sale by online research chemical vendors around this time. Information about the analysis of powdered samples has been disseminated including one sample that has apparently been sold as ketamine (EcstasyData.org 2018). Internet discussions suggest that 2-FDCK might be an active dissociative drug with potency comparable (or slightly more so) than ketamine. The analysis of a sample obtained from a test purchase (GC-MS and NMR) appeared consistent with the described structure (Wallach unpublished). Insufflation of 50 mg of analytically confirmed FDCK (salt unknown but suspected HCl, consumed over about an hour) induced dissociative effects with fluctuating tinnitus (personal communication). Although detailed pharmacological data on 2-FDCK could not be identified, Moghimi et al. (2014) stated that "preliminary animal tests on mice have shown that the resulting fluoroketamine has some advantages over ketamine in terms of the effective dose and the recovery time." However, further details were not included. A few other fluorinated β-keto-arylcyclohexylamines can be found discussed on online drug discussion forms including fluorexetamine (FXE) and 2-trifluoromethyl-2-deschloroketamine (2TFMDCK) (Fig. 2). More research is needed on these compounds.

4 Conclusions

The currently available data suggest that the 1,2-diarylethylamine- and β-keto-arylcyclohexylamine-based NPS show high to moderate affinities for the NMDAR where they also act as uncompetitive antagonists. In some cases, NMDAR affinity appears to correlate well with the dissociative properties in humans, whereas the 1,2-diarylethylamines evaluated show reduced potency in humans and animal models relative to their NMDAR affinity. The cause for this is unknown and warrants additional investigations although pharmacokinetic variables may be important. Furthermore, some non-NMDAR receptor interactions have been noted including affinities for and inhibition of monoamine reuptake transporters, as well as affinities for sigma receptors and in few cases also opioid receptor and α-adrenergic subtypes. The contribution of these mechanisms to the subjective effects of these compounds remains poorly understood, but it is possible they can contribute to the activity of individual compounds. Common clinical features reported from acute intoxication cases have included confusion, hallucination, dissociation, catatonia, euphoria, comatose states, and nystagmus but also hypertension and tachycardia. Other compounds that act through NMDAR known to cause dissociative effects are available from Internet retailers (e.g., memantine and D-cycloserine) but detailed information about their use and popularity is currently limited. Evolution of legislative control measures, market demand, and technology is likely to continue to change the research chemical market. Compared to other NPS classes, such as the synthetic cathinones or cannabinoid receptor agonists, the number of dissociative

drugs available on the open NPS market is comparatively small, but the potential for expanding the product catalogs is significant, which includes potential for research on drugs with potential clinical utility.

References

Aalto S, Hirvonen J, Kajander J, Scheinin H, Någren K, Vilkman H, Gustafsson L, Syvälahti E, Hietala J (2002) Ketamine does not decrease striatal dopamine D_2 receptor binding in man. Psychopharmacology 164:401–406

Abel KM, Allin MP, Hemsley DR, Geyer MA (2003) Low dose ketamine increases prepulse inhibition in healthy men. Neuropharmacology 44:729–737

Adamowicz P, Zuba D (2015) Fatal intoxication with methoxetamine. J Forensic Sci 60(Suppl 1): S264–S268

Adams JD Jr, Baillie TA, Trevor AJ, Castagnoli N Jr (1981) Studies on the biotransformation of ketamine. 1. Identification of metabolites produced in vitro from rat liver microsomal preparations. Biomed Mass Spectrom 8:527–538

Alvarez J-C, Fabresse N, Knapp A, El Hajj Sleiman I, Garnier R, Langrand J (2017) Identification and quantification of diphenidine in hair by LC-MS/MS after single administration. Toxicol Anal Clin 29:64–70

Amphoux A, Vialou V, Drescher E, Brüss M, Mannoury La Cour C, Rochat C, Millan MJ, Giros B, Bönisch H, Gautron S (2006) Differential pharmacological in vitro properties of organic cation transporters and regional distribution in rat brain. Neuropharmacology 50:941–952

Anis NA, Berry SC, Burton NR, Lodge D (1983) The dissociative anaesthetics, ketamine and phencyclidine, selectively reduce excitation of central mammalian neurons by N-methyl-aspartate. Br J Pharmacol 79:565–575

Anonymous (1960) Pharmaceutical compositions and methods for producing phenylcyclohexane compounds. Patent No. GB853775A. Parke Davis, Detroit

Anonymous (2007) Synthese von 2-Methylamino-2-phenylcyclohexanon (MPCH) [7063-30-1]. Last updated: 11 May 2007. http://www.lambdasyn.org/synfiles/mpch.htm. Accessed 26 Mar 2018

Anonymous (2014) The Big & Dandy Methoxmetamine/MXM Thread - V1: Note, this is not MXE! Bluelight. http://www.bluelight.org/vb/threads/732888-The-Big-amp-Dandy-Methoxmetamine-MXM-Thread-V1-Note-this-is-not-MXE! Accessed 24 Apr 2018

Anonymous (2015a) The Big & Dandy 2-Fluoroketamine Thread. Bluelight. http://www.bluelight.org/vb/threads/776753-The-Big-amp-Dandy-2-Fluoroketamine-Thread. Accessed 24 Apr 2018

Anonymous (2015b) Fluorolintane. https://www.ukchemicalresearch.org/Thread-Fluorolintane. Accessed 3 Feb 2018

Anonymous (2017) 2f-DCK vs DCK vs O-PCE, what do you prefer? Reddit. https://www.reddit.com/r/researchchemicals/comments/75iydc/2fdck_vs_dck_vs_opce_what_do_you_prefer/. Accessed 3 Feb 2018

Aspergren BD, Heinzelman RV (1963) Therapeutic 1-(1,2-diphenylethyl) pyrrolidine for the management of depression. Patent No. US3083139. Upjohn Company, Kalamazoo

Aspergren BD, Heinzelman RV (1964) Process for obtaining weight reduction. Patent No. US3134716. Upjohn Company, Kalamazoo

Azzaro AJ, Smith DJ (1977) The inhibitory action of ketamine HCl on [^{3}H]5-hydroxytryptamine accumulation by rat brain synaptosomal-rich fractions: comparison with [^{3}H]catecholamine and [^{3}H]γ-aminobutyric acid uptake. Neuropharmacology 16:349–356

Backberg M, Jonsson KH, Beck O, Helander A (2018) Investigation of drug products received for analysis in the Swedish STRIDA project on new psychoactive substances. Drug Test Anal 10:340–349

Beharry S, Gibbons S (2016) An overview of emerging and new psychoactive substances in the United Kingdom. Forensic Sci Int 267:25–34

Berger ML, Schweifer A, Rebernik P, Hammerschmidt F (2009) NMDA receptor affinities of 1,2-diphenylethylamine and 1-(1,2-diphenylethyl)piperidine enantiomers and of related compounds. Bioorg Med Chem 17:3456–3462

Berquist MD, Hyatt WS, Bauer-Erickson J, Gannon BM, Norwood AP, Fantegrossi WE (2017) Phencyclidine-like in vivo effects of methoxetamine in mice and rats. Neuropharmacology. https://doi.org/10.1016/j.neuropharm.2017.1008.1028

Boateng BO, Fever M, Edwards D, Petersson P, Euerby MR, Sutcliffe OB (2018) Chromatographic retention behaviour, modelling and optimization of a UHPLC-UV separation of the regioisomers of the Novel Psychoactive Substance (NPS) methoxphenidine (MXP). J Pharm Biomed Anal 153:238–247

Botanas CJ, de la Peña JB, Dela Peña IJ, Tampus R, Yoon R, Kim HJ, Lee YS, Jang CG, Cheong JH (2015) Methoxetamine, a ketamine derivative, produced conditioned place preference and was self-administered by rats: evidence of its abuse potential. Pharmacol Biochem Behav 133:31–36

Botanas CJ, Bryan de la Pena J, Custodio RJ, Joy Dela Pena I, Kim M, Woo T, Kim HJ, Kim HI, Chang Cho M, Lee YS, Cheong JH (2017) Methoxetamine produces rapid and sustained antidepressant effects probably via glutamatergic and serotonergic mechanisms. Neuropharmacology 126:121–127

Brunner H, Kagan HB, Kreutzer G (2003) Asymmetric catalysis. Part 153: metal-catalysed enantioselective α-ketol rearrangement. Tetrahedron Asymmetry 14:2177–2187

Caloro M, Calabro G, de Pisa E, Rosini E, Kotzalidis GD, Lonati D, Locatelli CA, Papa P, Schifano F, Girardi P (2018) Combined NMDA inhibitor use in a patient with multisubstance-induced psychotic disorder. J Addict Med. https://doi.org/10.1097/adm.0000000000000390

Campbell KN, Helbing CH, Florkowski MP, Campbell BK (1948) The reaction of Grignard reagents with Schiff bases. J Am Chem Soc 70:3868–3870

Can A, Zanos P, Moaddel R, Kang HJ, Dossou KS, Wainer IW, Cheer JF, Frost DO, Huang XP, Gould TD (2016) Effects of ketamine and ketamine metabolites on evoked striatal dopamine release, dopamine receptors, and monoamine transporters. J Pharmacol Exp Ther 359:159–170

Chambers RA, Bremner JD, Moghaddam B, Southwick SM, Charney DS, Krystal JH (1999) Glutamate and post-traumatic stress disorder: toward a psychobiology of dissociation. Semin Clin Neuropsychiatry 4:274–281

Champeau W, Eiden C, Gambier J, Peyriere H (2017) Methoxphenidine use disorder: first case notified to the French addictovigilance network. J Clin Psychopharmacol 37:376–377

Chen G (1969) The pharmacology of ketamine. In: Kreuscher H (ed) Ketamine: Bericht über das internationale Symposion am 23. und 24. Februar 1968 in Mainz. Springer, Berlin, Heidelberg, pp 1–11

Chen X, Shu S, Bayliss DA (2009) HCN1 channel subunits are a molecular substrate for hypnotic actions of ketamine. J Neurosci 29:600–609

Cheng HC, Long JP, Van Orden LS III, Cannon JG, O'Donnell JP (1976) Dopaminergic activity of some apomorphine analogs. Res Commun Chem Pathol Pharmacol 15:89–106

Chiamulera C, Armani F, Mutti A, Fattore L (2016) The ketamine analogue methoxetamine generalizes to ketamine discriminative stimulus in rats. Behav Pharmacol 27:204–210

Chodoff P, Stella JG (1966) Use of CI-581: a phencyclidine derivative for obstetric anesthesia. Anesth Analg 45:527–530

Chretien B, Bourgine J, Hamel Sénécal L, Bretaudeau-Deguigne M, Boels D, Lelong-Boulouard V, Le Boisselier R (2018) Severe serotonin syndrome in an autistic new psychoactive substance user after consumption of pills containing methoxphenidine and α-methyltryptamine. J Clin Psychopharmacol 38:94–96

Christiaen A (1924) Contribution à l'étude de la réaction des organo-magnésiens sur les nitriles. Les nitriles α amines. Bull Soc Chim Belg 33:483–490

Chu PS, Kwok SC, Lam KM, Chu TY, Chan SW, Man CW, Ma WK, Chui KL, Yiu MK, Chan YC, Tse ML, Lau FL (2007) 'Street ketamine'-associated bladder dysfunction: a report of ten cases. Hong Kong Med J 13:311–313

Cilia J, Hatcher P, Reavill C, Jones DN (2007) (±)Ketamine-induced prepulse inhibition deficits of an acoustic startle response in rats are not reversed by antipsychotics. J Psychopharmacol 21:302–311

Clements JA, Nimmo WS (1981) Pharmacokinetics and analgesic effect of ketamine in man. Br J Anaesth 53:27–30

Cohen ML, Trevor AJ (1974) On the cerebral accumulation of ketamine and the relationship between metabolism of the drug and its pharmacological effects. J Pharmacol Exp Ther 189:351–358

Colestock T, Wallach J, Mansi M, Filemban N, Morris H, Elliott SP, Westphal F, Brandt SD, Adejare A (2018) Syntheses, analytical and pharmacological characterizations of the 'legal high' 4-[1-(3-methoxyphenyl)cyclohexyl]morpholine (3-MeO-PCMo) and analogues. Drug Test Anal 10:272–283

Coppola M, Mondola R (2012) Methoxetamine: from drug of abuse to rapid-acting antidepressant. Med Hypotheses 79:504–507

Coppola M, Mondola R (2013) Is methoxydine a new rapid acting antidepressant for the treatment of depression in alcoholics? Med Hypotheses 81:10–14

Corazza O, Assi S, Schifano F (2013) From "Special K" to "Special M": the evolution of the recreational use of ketamine and methoxetamine. CNS Neurosci Ther 19:454–460

Corssen G, Domino EF (1966) Dissociative anesthesia: further pharmacologic studies and first clinical experience with the phencyclidine derivative CI-581. Anesth Analg 45:29–40

Critchlow DG (2006) A case of ketamine dependence with discontinuation symptoms. Addiction 101:1212–1213

Cumming JF (1976) The development of an acute tolerance to ketamine. Anesth Analg 55:788–791

Dargan PI, Tang HC, Liang W, Wood DM, Yew DT (2014) Three months of methoxetamine administration is associated with significant bladder and renal toxicity in mice. Clin Toxicol (Phila) 52:176–180

Davies SN, Alford ST, Coan EJ, Lester RA, Collingridge GL (1988) Ketamine blocks an NMDA receptor-mediated component of synaptic transmission in rat hippocampus in a voltage-dependent manner. Neurosci Lett 92:213–217

Dayton PG, Stiller RL, Cook DR, Perel JM (1983) The binding of ketamine to plasma proteins: emphasis on human plasma. Eur J Clin Pharmacol 24:825–831

de Bruin NM, Ellenbroek BA, Cools AR, Coenen AM, van Luijtelaar EL (1999) Differential effects of ketamine on gating of auditory evoked potentials and prepulse inhibition in rats. Psychopharmacology 142:9–17

De Luca MT, Badiani A (2011) Ketamine self-administration in the rat: evidence for a critical role of setting. Psychopharmacology 214:549–556

Dodds EC, Lawson W, Williams PC (1944) Morphine-like properties of diphenylethylamine and related compounds. Proc R Soc Lond B Biol Sci 132:119–132

Dodds EC, Lawson W, Simpson SA, Williams PC (1945) Testing diphenylethylamine compounds for analgesic action. J Physiol 104:47–51

Domino EF (2010) Taming the ketamine tiger. Anesthesiology 113:678–684

Domino EF (ed) (2018) Status of ketamine in anesthesiology [reprint from 1990]. NPP Books, Arlington

Domino EF, Chodoff P, Corssen G (1965) Pharmacologic effects of CI-581, a new dissociative anesthetic, in man. Clin Pharmacol Ther 6:279–291

Ebert B, Mikkelsen S, Thorkildsen C, Borgbjerg FM (1997) Norketamine, the main metabolite of ketamine, is a non-competitive NMDA receptor antagonist in the rat cortex and spinal cord. Eur J Pharmacol 333:99–104

EcstasyData.org (2018) https://www.ecstasydata.org/results.php?start=0&search_field=all&s=deschloroketamine. Accessed 2 Apr 2018

Elliott SP, Brandt SD, Freeman S, Archer RP (2013) AMT (3-(2-aminopropyl)indole) and 5-IT (5-(2-aminopropyl)indole): an analytical challenge and implications for forensic analysis. Drug Test Anal 5:196–202

Elliott SP, Brandt SD, Wallach J, Morris H, Kavanagh PV (2015) First reported fatalities associated with the 'research chemical' 2-methoxydiphenidine. J Anal Toxicol 39:287–293

Elliott S, Sedefov R, Evans-Brown M (2018) Assessing the toxicological significance of new psychoactive substances in fatalities. Drug Test Anal 10:120–126

EMCDDA (2014) Methoxetamine. Report on the risk assessment of 2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone (methoxetamine) in the framework of the Council Decision on new psychoactive substances. EMCDDA, Lisbon. http://www.emcdda.europa.eu/system/files/publications/775/TDAK14004ENN_480922.pdf. Accessed 3 Feb 2018

EMCDDA–Europol (2011) EMCDDA–Europol 2010 annual report on the implementation of Council Decision 2005/387/JHA. In accordance with Article 10 of Council Decision 2005/387/JHA on the information exchange, risk assessment and control of new psychoactive substances. EMCDDA, Lisbon. http://www.emcdda.europa.eu/system/files/publications/644/EMCDDA-Europol_Annual_Report_2010A_281336.pdf. Accessed 3 Feb 2018

EMCDDA–Europol (2013) New drugs in Europe, 2012. EMCDDA–Europol 2012 annual report on the implementation of Council Decision 2005/387/JHA. In accordance with Article 10 of Council Decision 2005/387/JHA on the information exchange, risk assessment and control of new psychoactive substances. EMCDDA, Lisbon. http://www.emcdda.europa.eu/system/files/publications/734/EMCDDA-Europol_2012_Annual_Report_final_439477.pdf. Accessed 3 Feb 2018

EMCDDA–Europol (2014) EMCDDA–Europol 2013 annual report on the implementation of Council Decision 2005/387/JHA. In accordance with Article 10 of Council Decision 2005/387/JHA on the information exchange, risk assessment and control of new psychoactive substances. EMCDDA, Lisbon. http://www.emcdda.europa.eu/system/files/publications/814/TDAN14001ENN_475519.pdf. Accessed 3 Feb 2018

EMCDDA–Europol (2015) EMCDDA–Europol 2014 annual report on the implementation of Council Decision 2005/387/JHA. In accordance with Article 10 of Council Decision 2005/387/JHA on the information exchange, risk assessment and control of new psychoactive substances. EMCDDA, Lisbon. http://www.emcdda.europa.eu/system/files/publications/1018/TDAN15001ENN.pdf. Accessed 3 Feb 2018

EMCDDA–Europol (2016) EMCDDA–Europol 2015 annual report on the implementation of Council Decision 2005/387/JHA. In accordance with Article 10 of Council Decision 2005/387/JHA on the information exchange, risk assessment and control of new psychoactive substances. EMCDDA, Lisbon. http://www.emcdda.europa.eu/system/files/publications/2880/TDAS16001ENN.pdf. Accessed 3 Feb 2018

EMCDDA–Europol (2017) EMCDDA–Europol 2016 annual report on the implementation of Council Decision 2005/387/JHA. In accordance with Article 10 of Council Decision 2005/387/JHA on the information exchange, risk assessment and control of new psychoactive substances. EMCDDA, Lisbon. http://www.emcdda.europa.eu/system/files/publications/4724/TDAN17001ENN_PDFWEB.pdf. Accessed 3 Feb 2018

Energycontrol (2015) Alerta: descloroketamina vendida como ketamina en Barcelona. https://energycontrol.org/analisis-de-sustancias/resultados/alertas/560-alerta-descloroketamina-vendida-como-ketamina-en-barcelona.html. Accessed 3 Feb 2018

Fourcade EW, Lapidus KAB (2016) The basic and clinical pharmacology of ketamine. In: Mathew SJ, Zarate JCA (eds) Ketamine for treatment-resistant depression: the first decade of progress. Springer, Cham, pp 13–29. https://doi.org/10.1007/978-3-319-42925-0_2

Frankiewicz T, Potier B, Bashir ZI, Collingridge GL, Parsons CG (1996) Effects of memantine and MK-801 on NMDA-induced currents in cultured neurones and on synaptic transmission and LTP in area CA1 of rat hippocampal slices. Br J Pharmacol 117:689–697

Fray MJ, Bish G, Brown AD, Fish PV, Stobie A, Wakenhut F, Whitlock GA (2006a) N-(1,2-Diphenylethyl)piperazines: a new class of dual serotonin/noradrenaline reuptake inhibitor. Bioorg Med Chem Lett 16:4345–4348

Fray MJ, Bish G, Fish PV, Stobie A, Wakenhut F, Whitlock GA (2006b) Structure-activity relationships of N-substituted piperazine amine reuptake inhibitors. Bioorg Med Chem Lett 16:4349–4353

Frison G, Zamengo L, Zancanaro F, Tisato F, Traldi P (2016) Characterization of the designer drug deschloroketamine (2-methylamino-2-phenylcyclohexanone) by gas chromatography/mass spectrometry, liquid chromatography/high-resolution mass spectrometry, multistage mass spectrometry, and nuclear magnetic resonance. Rapid Commun Mass Spectrom 30:151–160

Frohlich J, Van Horn JD (2014) Reviewing the ketamine model for schizophrenia. J Psychopharmacol 28:287–302

Garcia Ruano JL, Parra A, Aleman J, Yuste F, Mastranzo VM (2009) Monoalkylation of primary amines and N-sulfinylamides. Chem Commun 404–406

Garcia LS, Comim CM, Valvassori SS, Reus GZ, Barbosa LM, Andreazza AC, Stertz L, Fries GR, Gavioli EC, Kapczinski F, Quevedo J (2008) Acute administration of ketamine induces antidepressant-like effects in the forced swimming test and increases BDNF levels in the rat hippocampus. Prog Neuro-Psychopharmacol Biol Psychiatry 32:140–144

Gerace E, Bovetto E, Corcia DD, Vincenti M, Salomone A (2017) A case of nonfatal intoxication associated with the recreational use of diphenidine. J Forensic Sci 62:1107–1111

Geyer PM, Hulme MC, Irving JPB, Thompson PD, Ashton RN, Lee RJ, Johnson L, Marron J, Banks CE, Sutcliffe OB (2016) Guilty by dissociation – development of gas chromatography–mass spectrometry (GC-MS) and other rapid screening methods for the analysis of 13 diphenidine-derived new psychoactive substances (NPSs). Anal Bioanal Chem 408:8467–8481

Ghosh P, Bolt AG, Mrongovius RI (1978) 1,2-Diphenylethylamines as potential non-stimulant anorectics. Arzneimittelforschung 28:1561–1564

Goodson LH, Christopher H (1950) Diphenylethylamines.I. The preparation of tertiary amines by the Grignard reaction. J Am Chem Soc 72:358–362

Goodson LH, Wiegand CJW, Splitter JS (1946) Analgesics. I. N-Alkylated 1,2-diphenylethylamines prepared by the Leuckart reaction. J Am Chem Soc 68:2174–2175

Gouzoulis-Mayfrank E, Heekeren K, Neukirch A, Stoll M, Stock C, Obradovic M, Kovar KA (2005) Psychological effects of (S)-ketamine and N,N-dimethyltryptamine (DMT): a double-blind, cross-over study in healthy volunteers. Pharmacopsychiatry 38:301–311

Grant IS, Nimmo WS, Clements JA (1981) Pharmacokinetics and analgesic effects of i.m. and oral ketamine. Br J Anaesth 53:805–810

Gray NM, Cheng BK (1989) 1,2-Diarylethylamines for treatment of neurotoxic injury. Patent No. EP346791A1. G.D. Searle and Co., Chicago

Grumann C, Vogt S, Huppertz LM, Moosmann B, Franz F, Angerer V, Kramer L, Auwärter V (2016) Drowning due to an intoxication involving the designer drug methoxphenidine – a case report. In: Poster. 54th annual meeting of TIAFT, Brisbane, 28 Aug–1 Sept. https://www.uniklinik-freiburg.de/fileadmin/mediapool/08_institute/rechtsmedizin/pdf/Poster_2016/Grumann_-_Tiaft_2016.pdf. Accessed 3 Feb 2018

Hajkova K, Jurasek B, Sykora D, Palenicek T, Miksatkova P, Kuchar M (2016) Salting-out-assisted liquid-liquid extraction as a suitable approach for determination of methoxetamine in large sets of tissue samples. Anal Bioanal Chem 408:1171–1181

Halberstadt AL, Slepak N, Hyun J, Buell MR, Powell SB (2016) The novel ketamine analog methoxetamine produces dissociative-like behavioral effects in rodents. Psychopharmacology 233:1215–1225

Hansch C, Bjorkroth JP, Leo A (1987) Hydrophobicity and central nervous system agents: on the principle of minimal hydrophobicity in drug design. J Pharm Sci 76:663–687

Harvey M, Sleigh J, Voss L, Jose J, Gamage S, Pruijn F, Liyanage S, Denny W (2015) Development of rapidly metabolized and ultra-short-acting ketamine analogs. Anesth Analg 121:925–933

Hasegawa K, Wurita A, Minakata K, Gonmori K, Nozawa H, Yamagishi I, Watanabe K, Suzuki O (2015) Postmortem distribution of AB-CHMINACA, 5-fluoro-AMB, and diphenidine in body fluids and solid tissues in a fatal poisoning case: usefulness of adipose tissue for detection of the drugs in unchanged forms. Forensic Toxicol 33:45–53

Hearne E, Van Hout MC (2016) "Trip-sitting" in the black hole: a netnographic study of dissociation and indigenous harm reduction. J Psychoactive Drugs 48:233–242

Heekeren K, Neukirch A, Daumann J, Stoll M, Obradovic M, Kovar KA, Geyer MA, Gouzoulis-Mayfrank E (2007) Prepulse inhibition of the startle reflex and its attentional modulation in the human S-ketamine and N,N-dimethyltryptamine (DMT) models of psychosis. J Psychopharmacol 21:312–320

Heinzelman RV, Aspergren BD (1953) Compounds containing the pyrrolidine ring. Analogs of sympathomimetic amines. J Am Chem Soc 75:3409–3413

Helander A, Beck O, Bäckberg M (2015) Intoxications by the dissociative new psychoactive substances diphenidine and methoxphenidine. Clin Toxicol (Phila) 53:446–453

Hesp KD, Stradiotto M (2010) Stereo- and regioselective gold-catalyzed hydroamination of internal alkynes with dialkylamines. J Am Chem Soc 132:18026–18029

Hijazi Y, Boulieu R (2002) Contribution of CYP3A4, CYP2B6, and CYP2C9 isoforms to N-demethylation of ketamine in human liver microsomes. Drug Metab Dispos 30:853–858

Hirota K, Lambert DG (1996) Ketamine: its mechanism(s) of action and unusual clinical uses. Br J Anaesth 77:441–444

Hirota K, Okawa H, Appadu BL, Grandy DK, Devi LA, Lambert DG (1999) Stereoselective interaction of ketamine with recombinant μ, κ, and δ opioid receptors expressed in Chinese hamster ovary cells. Anesthesiology 90:174–182

Ho JH, Dargan PI (2017) Arylcyclohexamines: ketamine, phencyclidine, and analogues. In: Brent J, Burkhart K, Dargan P et al (eds) Critical care toxicology: diagnosis and management of the critically poisoned patient. Springer, Cham, pp 1439–1484

Hofer KE, Grager B, Müller DM, Rauber-Lüthy C, Kupferschmidt H, Rentsch KM, Ceschi A (2012) Ketamine-like effects after recreational use of methoxetamine. Ann Emerg Med 60:97–99

Hofer KE, Degrandi C, Müller DM, Zürrer-Härdi U, Wahl S, Rauber-Lüthy C, Ceschi A (2014) Acute toxicity associated with the recreational use of the novel dissociative psychoactive substance methoxphenidine. Clin Toxicol 52:1288–1291

Holtman JR Jr, Crooks PA, Johnson-Hardy JK, Hojomat M, Kleven M, Wala EP (2008) Effects of norketamine enantiomers in rodent models of persistent pain. Pharmacol Biochem Behav 90:676–685

Hondebrink L, Verboven AHA, Drega WS, Schmeink S, de Groot M, van Kleef R, Wijnolts FMJ, de Groot A, Meulenbelt J, Westerink RHS (2016) Neurotoxicity screening of (illicit) drugs using novel methods for analysis of microelectrode array (MEA) recordings. Neurotoxicology 55:1–9

Hondebrink L, Kasteel EEJ, Tukker AM, Wijnolts FMJ, Verboven AHA, Westerink RHS (2017) Neuropharmacological characterization of the new psychoactive substance methoxetamine. Neuropharmacology 123:1–9

Hondebrink L, Zwartsen A, Westerink RHS (2018) Effect fingerprinting of new psychoactive substances (NPS): what can we learn from in vitro data? Pharmacol Ther 182:193–224

Horsley RR, Lhotkova E, Hajkova K, Jurasek B, Kuchar M, Palenicek T (2016) Detailed pharmacological evaluation of methoxetamine (MXE), a novel psychoactive ketamine analogue – behavioural, pharmacokinetic and metabolic studies in the Wistar rat. Brain Res Bull 126:102–110

Hungarian Institute for Forensic Science (2016) Analytical data for Deschloroketamine. Hungarian Institute for Forensic Science. https://www.policija.si/apps/nfl_response_web/0_Analytical_Reports_final/Deschloroketamine-ID-HIFS003_rpt.pdf. Accessed 2 Apr 2018

Hurt PH, Ritchie EC (1994) A case of ketamine dependence. Am J Psychiatry 151:779

Hustveit O, Maurset A, Øye I (1995) Interaction of the chiral forms of ketamine with opioid, phencyclidine, sigma and muscarinic receptors. Pharmacol Toxicol 77:355–359

Jansen KLR (2004) Ketamine: dreams and realities. Multidisciplinary Association for Psychedelic Studies, Sarasota. https://www.maps.org/images/pdf/books/K-DreamsKJansenMAPS.pdf. Accessed 8 Feb 2018

Jones LE, Stewart A, Peters KL, McNaul M, Speers SJ, Fletcher NC, Bell SE (2016) Infrared and Raman screening of seized novel psychoactive substances: a large scale study of >200 samples. Analyst 141:902–909

Jordan S, Chen R, Fernalld R, Johnson J, Regardie K, Kambayashi J, Tadori Y, Kitagawa H, Kikuchi T (2006) In vitro biochemical evidence that the psychotomimetics phencyclidine, ketamine and dizocilpine (MK-801) are inactive at cloned human and rat dopamine D_2 receptors. Eur J Pharmacol 540:53–56

Kaizaki-Mitsumoto A, Noguchi N, Yamaguchi S, Odanaka Y, Matsubayashi S, Kumamoto H, Fukuhara K, Funada M, Wada K, Numazawa S (2016) Three 25-NBOMe-type drugs, three other phenethylamine-type drugs (25I-NBMD, RH34, and escaline), eight cathinone derivatives, and a phencyclidine analog MMXE, newly identified in ingredients of drug products before they were sold on the drug market. Forensic Toxicol 34:108–114

Kamenka JM, Geneste P (1981) Synthesis, conformation, and physical properties of phencyclidine and its derivatives. In: Domino EF (ed) PCP (phencyclidine): historical and current perspectives. NPP Books, Ann Arbor, pp 47–82

Kang H, Park P, Bortolotto ZA, Brandt SD, Colestock T, Wallach J, Collingridge GL, Lodge D (2017) Ephenidine: a new psychoactive agent with ketamine-like NMDA receptor antagonist properties. Neuropharmacology 112:144–149

Kapur S, Seeman P (2002) NMDA receptor antagonists ketamine and PCP have direct effects on the dopamine D_2 and serotonin 5-HT_2 receptors-implications for models of schizophrenia. Mol Psychiatry 7:837–844

Kasé Y, Yuizono T, Muto M (1963) Piperidino groups in antitussive activity. J Med Chem 6:118–122

Katalinic N, Lai R, Somogyi A, Mitchell PB, Glue P, Loo CK (2013) Ketamine as a new treatment for depression: a review of its efficacy and adverse effects. Aust N Z J Psychiatry 47:710–727

Keiser M, Hasan M, Oswald S (2018) Affinity of ketamine to clinically relevant transporters. Mol Pharm 15:326–331

Kharasch ED, Labroo R (1992) Metabolism of ketamine stereoisomers by human liver microsomes. Anesthesiology 77:1201–1207

Kinoshita H, Tanaka N, Takakura A, Abe H, Kumihashi M, Shibayama T, Jamal M, Ito A, Tsutsui K, Kimura S, Iwase H, Ameno K (2017) An autopsy case of death by combined use of benzodiazepines and diphenidine. Soud Lek 62:40–43

Kjellgren A, Jonsson K (2013) Methoxetamine (MXE) – a phenomenological study of experiences induced by a "legal high" from the internet. J Psychoactive Drugs 45:276–286

Kohrs R, Durieux ME (1998) Ketamine: teaching an old drug new tricks. Anesth Analg 87:1186–1193

Koike H, Chaki S (2014) Requirement of AMPA receptor stimulation for the sustained antidepressant activity of ketamine and LY341495 during the forced swim test in rats. Behav Brain Res 271:111–115

Koinig H, Marhofer P, Krenn CG, Klimscha W, Wildling E, Erlacher W, Nikolic A, Turnheim K, Semsroth M (2000) Analgesic effects of caudal and intramuscular *S*(+)-ketamine in children. Anesthesiology 93:976–980

Kokkinou M, Ashok AH, Howes OD (2018) The effects of ketamine on dopaminergic function: meta-analysis and review of the implications for neuropsychiatric disorders. Mol Psychiatry 23:59–69

Kreuscher H (ed) (1969) Ketamine. Bericht über das internationale Symposion am 23. und 24. Februar 1968 in Mainz. Springer, Berlin

Krupitsky EM, Burakov AM, Romanova TN, Grinenko NI, Grinenko AY, Fletcher J, Petrakis IL, Krystal JH (2001) Attenuation of ketamine effects by nimodipine pretreatment in recovering ethanol dependent men: psychopharmacologic implications of the interaction of NMDA and L-type calcium channel antagonists. Neuropsychopharmacology 25:936–947

Krupitsky EM, Burakov AM, Dunaevsky IV, Romanova TN, Slavina TY, Grinenko AY (2007) Single versus repeated sessions of ketamine-assisted psychotherapy for people with heroin dependence. J Psychoactive Drugs 39:13–19

Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, Heninger GR, Bowers MB Jr, Charney DS (1994) Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch Gen Psychiatry 51:199–214

Kudo K, Usumoto Y, Kikura-Hanajiri R, Sameshima N, Tsuji A, Ikeda N (2015) A fatal case of poisoning related to new cathinone designer drugs, 4-methoxy PV8, PV9, and 4-methoxy PV9, and a dissociative agent, diphenidine. Leg Med (Tokyo) 17:421–426

Kusano M, Zaitsu K, Taki K, Hisatsune K, Nakajima J, Moriyasu T, Asano T, Hayashi Y, Tsuchihashi H, Ishii A (2017) Fatal intoxication by 5F-ADB and diphenidine: detection, quantification, and investigation of their main metabolic pathways in humans by LC/MS/MS and LC/Q-TOFMS. Drug Test Anal. https://doi.org/10.1002/dta.2215

Laher I, Zhang X, Leung PC, Liang W (2015) Diverse pharmacological properties of ketamine. In: Yew DT (ed) Ketamine. Use and abuse. CRC Press, Boca Raton, pp 37–63

Lahti AC, Koffel B, LaPorte D, Tamminga CA (1995) Subanesthetic doses of ketamine stimulate psychosis in schizophrenia. Neuropsychopharmacology 13:9–19

Lalonde BR, Wallage HR (2004) Postmortem blood ketamine distribution in two fatalities. J Anal Toxicol 28:71–74

Lam RP, Yip WL, Tsui MS, Ng SW, Ching CK, Mak TW (2016) Severe rhabdomyolysis and acute kidney injury associated with methoxphenidine. Clin Toxicol (Phila) 54:464–465

Lawn W, Borschmann R, Cottrell A, Winstock A (2016) Methoxetamine: prevalence of use in the USA and UK and associated urinary problems. J Subst Use 21:115–120

Le Gall E, Troupel M, Nedelec JY (2006) One-step three-component coupling of aromatic organozinc reagents, secondary amines, and aromatic aldehydes into functionalized diarylmethylamines. Tetrahedron 62:9953–9965

Leander JD, Rathbun RC, Zimmerman DM (1988) Anticonvulsant effects of phencyclidine-like drugs: relation to N-methyl-D-aspartic acid antagonism. Brain Res 454:368–372

Li Q, Man Chan W, Rudd JA, Mei Wang C, Lam PYH, Mun Wai MS, Wood DM, Dargan PI, Yew DT (2013a) Ketamine. In: Dargan PI, Wood DM (eds) Novel psychoactive substances. Academic Press, Boston, pp 285–316

Li Y, Coller JK, Hutchinson MR, Klein K, Zanger UM, Stanley NJ, Abell AD, Somogyi AA (2013b) The CYP2B6*6 allele significantly alters the N-demethylation of ketamine enantiomers in vitro. Drug Metab Dispos 41:1264–1272

Li Y, Jackson KA, Slon B, Hardy JR, Franco M, William L, Poon P, Coller JK, Hutchinson MR, Currow DC, Somogyi AA (2015) CYP2B6*6 allele and age substantially reduce steady-state ketamine clearance in chronic pain patients: impact on adverse effects. Br J Clin Pharmacol 80:276–284

Licata M, Pierini G, Popoli G (1994) A fatal ketamine poisoning. J Forensic Sci 39:1314–1320

Lilly JC (1996) The scientist. A metaphysical autobiography, 3rd edn. Ronin Publishing, Oakland

Lim DK (2003) Ketamine associated psychedelic effects and dependence. Singap Med J 44:31–34

Lin F, He Y, Zhang L, Zhang M, Zhang Y, Wen C (2015) Assessment of the effect of ketamine on cytochrome P450 isoforms activity in rats by cocktail method. Int J Clin Exp Med 8:4335–4341

Livingston A, Waterman AE (1978) The development of tolerance to ketamine in rats and the significance of hepatic metabolism. Br J Pharmacol 64:63–69

Lodge D, Mercier MS (2015) Ketamine and phencyclidine: the good, the bad and the unexpected. Br J Pharmacol 172:4254–4276

Luethi D, Hoener MC, Liechti ME (2018) Effects of the new psychoactive substances diclofensine, diphenidine, and methoxphenidine on monoaminergic systems. Eur J Pharmacol 819:242–247

MacDonald JF, Miljkovic Z, Pennefather P (1987) Use-dependent block of excitatory amino acid currents in cultured neurons by ketamine. J Neurophysiol 58:251–266

Machado-Vieira R, Henter ID, Zarate CA Jr (2017) New targets for rapid antidepressant action. Prog Neurobiol 152:21–37

MacLennan FM (1982) Ketamine tolerance and hallucinations in children. Anaesthesia 37:1214–1215

Maixner J, Jurásek B, Kohout M, Kuchař M, Kačer P (2017) X-ray powder diffraction data for (S)-deschloroketamine hydrochloride, C13H18ClNO. Powder Diffract 32:193–195

Malhotra AK, Pinals DA, Weingartner H, Sirocco K, Missar CD, Pickar D, Breier A (1996) NMDA receptor function and human cognition: the effects of ketamine in healthy volunteers. Neuropsychopharmacology 14:301–307

Marcsekova K, Wegener B, Doye S (2005) Ind2TiMe2-catalyzed addition of methyl- and ethylamine to alkynes. Eur J Org Chem 4843–4851

Marietta MP, White PF, Pudwill CR, Way WL, Trevor AJ (1976) Biodisposition of ketamine in the rat: self-induction of metabolism. J Pharmacol Exp Ther 196:536–544

Maskell KF, Bailey ML, Rose SR (2016) Self medication with methoxetamine as an analgesic resulting in significant toxicity. Pain Med 17:1773–1775

Massmann V, Edemir B, Schlatter E, Al-Monajjed R, Harrach S, Klassen P, Holle SK, Sindic A, Dobrivojevic M, Pavenstädt H, Ciarimboli G (2014) The organic cation transporter 3 (OCT3) as molecular target of psychotropic drugs: transport characteristics and acute regulation of cloned murine OCT3. Pflugers Arch - Eur J Physiol 466:517–527

McCarthy DA (1981) History of the development of cataleptoid anesthetics of the phencyclidine type. In: Domino EF (ed) PCP (phencyclidine): historical and current perspectives. NPP Books, Ann Arbor, pp 17–24

McCarthy DA, Chen G, Kaump DH, Ensor C (1965) General anesthetic and other pharmacological properties of 2-(O-chlorophenyl)-2-methylamino cyclohexanone HCl (CI-581). J Clin Pharmacol 5:21–33

McLaughlin G, Morris N, Kavanagh PV, Power JD, O'Brien J, Talbot B, Elliott SP, Wallach J, Hoang K, Morris H, Brandt SD (2016) Test purchase, synthesis, and characterization of 2-methoxydiphenidine (MXP) and differentiation from its meta- and para-substituted isomers. Drug Test Anal 8:98–109

Mealing GA, Lanthorn TH, Small DL, Murray RJ, Mattes KC, Comas TM, Morley P (2001) Structural modifications to an N-methyl-D-aspartate receptor antagonist result in large differences in trapping block. J Pharmacol Exp Ther 297:906–914

Menzies EL, Hudson SC, Dargan PI, Parkin MC, Wood DM, Kicman AT (2014) Characterizing metabolites and potential metabolic pathways for the novel psychoactive substance methoxetamine. Drug Test Anal 6:506–515

Meyer MR, Bach M, Welter J, Bovens M, Turcant A, Maurer HH (2013a) Ketamine-derived designer drug methoxetamine: metabolism including isoenzyme kinetics and toxicological detectability using GC-MS and LC-(HR-)MS^n. Anal Bioanal Chem 405:6307–6321

Meyer MR, Orschiedt T, Maurer HH (2013b) Michaelis-Menten kinetic analysis of drugs of abuse to estimate their affinity to human P-glycoprotein. Toxicol Lett 217:137–142

Minakata K, Yamagishi I, Nozawa H, Hasegawa K, Wurita A, Gonmori K, Suzuki M, Watanabe K, Suzuki O (2015) Diphenidine and its metabolites in blood and urine analyzed by MALDI-Q-TOF mass spectrometry. Forensic Toxicol 33:402–408

Mion G, Villevieille T (2013) Ketamine pharmacology: an update (pharmacodynamics and molecular aspects, recent findings). CNS Neurosci Ther 19:370–380

Moaddel R, Venkata SL, Tanga MJ, Bupp JE, Green CE, Iyer L, Furimsky A, Goldberg ME, Torjman MC, Wainer IW (2010) A parallel chiral-achiral liquid chromatographic method for the determination of the stereoisomers of ketamine and ketamine metabolites in the plasma and urine of patients with complex regional pain syndrome. Talanta 82:1892–1904

Moghimi A, Rahmani S, Zare R, Sadeghzadeh M (2014) Synthesis of 2-(2-fluorophenyl)-2-methylamino-cyclohexanone as a new ketamine derivative. Synth Commun 44:2021–2028

Moore KA, Kilbane EM, Jones R, Kunsman GW, Levine B, Smith M (1997) Tissue distribution of ketamine in a mixed drug fatality. J Forensic Sci 42:1183–1185

Moreton JE, Meisch RA, Stark L, Thompson T (1977) Ketamine self-administration by the rhesus monkey. J Pharmacol Exp Ther 203:303–309

Morgan CJ, Curran HV (2012) Ketamine use: a review. Addiction (Abingdon, England) 107:27–38

Morris H (2011) Interview with a ketamine chemist or to be more precise, an arylcyclohexylamine chemist. Vice Mag 18:98–101

Morris H, Wallach J (2014) From PCP to MXE: a comprehensive review of the non-medical use of dissociative drugs. Drug Test Anal 6:614–632

Mutti A, Aroni S, Fadda P, Padovani L, Mancini L, Collu R, Muntoni AL, Fattore L, Chiamulera C (2016) The ketamine-like compound methoxetamine substitutes for ketamine in the self-administration paradigm and enhances mesolimbic dopaminergic transmission. Psychopharmacology 233:2241–2251

National Slovenian Forensic Laboratory (2016) Analytical report. Fluorolintane (C18H20FN). 1-(1-(2-fluorophenyl)-2-phenylethyl)pyrrolidine. National Slovenian Forensic Laboratory. https://www.policija.si/apps/nfl_response_web/0_Analytical_Reports_final/FLUOROLINTANE-ID-1420-15-report_final.pdf. Accessed 3 Feb 2018

Newcomer JW, Farber NB, Jevtovic-Todorovic V, Selke G, Melson AK, Hershey T, Craft S, Olney JW (1999) Ketamine-induced NMDA receptor hypofunction as a model of memory impairment and psychosis. Neuropsychopharmacology 20:106–118

Ng SH, Tse ML, Ng HW, Lau FL (2010) Emergency department presentation of ketamine abusers in Hong Kong: a review of 233 cases. Hong Kong Med J 16:6–11

Niciu MJ, Henter ID, Luckenbaugh DA, Zarate CA Jr, Charney DS (2014) Glutamate receptor antagonists as fast-acting therapeutic alternatives for the treatment of depression: ketamine and other compounds. Annu Rev Pharmacol Toxicol 54:119–139

Nishimura M, Sato K (1999) Ketamine stereoselectively inhibits rat dopamine transporter. Neurosci Lett 274:131–134

Nishimura M, Sato K, Okada T, Yoshiya I, Schloss P, Shimada S, Tohyama M (1998) Ketamine inhibits monoamine transporters expressed in human embryonic kidney 293 cells. Anesthesiology 88:768–774

Novelli A, Huidobro H (1963) Analogues <<ouverts>> de la papavérine. Activité spasmolytique type papavérine des dériveé de la 1,2(bis-diphényl)-éthylamine. Ann Pharm Fr 21:821–827

Oye I, Hustveit O, Maurset A, Ratti Moberg E, Paulsen O, Skoglund LA (1991) The chiral forms of ketamine as probes for NMDA receptor functions in humans. In: Kameyama T, Nabeshima T, Domino EF (eds) NMDA receptor related agents: biochemistry, pharmacology and behavior. NPP Books, Ann Arbor, pp 381–389

Oye I, Paulsen O, Maurset A (1992) Effects of ketamine on sensory perception: evidence for a role of N-methyl-D-aspartate receptors. J Pharmacol Exp Ther 260:1209–1213

Pal HR, Berry N, Kumar R, Ray R (2002) Ketamine dependence. Anaesth Intensive Care 30:382–384

Palmer GC, Hutchison JB (1997) Preclinical and clinical aspects of remacemide hydrochloride. In: Herrling PL (ed) Excitatory amino acids. Clinical results with antagonists. Academic Press, San Diego, pp 109–120

Parsons CG, Quack G, Bresink I, Baran L, Przegalinski E, Kostowski W, Krzascik P, Hartmann S, Danysz W (1995) Comparison of the potency, kinetics and voltage-dependency of a series of uncompetitive NMDA receptor antagonists in vitro with anticonvulsive and motor impairment activity in vivo. Neuropharmacology 34:1239–1258

Pomarol-Clotet E, Honey GD, Murray GK, Corlett PR, Absalom AR, Lee M, McKenna PJ, Bullmore ET, Fletcher PC (2006) Psychological effects of ketamine in healthy volunteers: phenomenological study. Br J Psychiatry 189:173–179

Preiss D, Tatar A (1995) Verwendung von 2-Methylamino-2-phenylcyclohexanon zur Behandlung von Bakterien-, Pilz-, Virus-, oder Protozoeninfektionen und zur Immunomodulation. Patent No. DE4409671. Berlin

Quirion R, Hammer RP Jr, Herkenham M, Pert CB (1981) Phencyclidine (angel dust)/sigma "opiate" receptor: visualization by tritium-sensitive film. Proc Natl Acad Sci U S A 78:5881–5885

Rao LK, Flaker AM, Friedel CC, Kharasch ED (2016) Role of cytochrome P4502B6 polymorphisms in ketamine metabolism and clearance. Anesthesiology 125:1103–1112

Ribeiro PO, Tome AR, Silva HB, Cunha RA, Antunes LM (2014) Clinically relevant concentrations of ketamine mainly affect long-term potentiation rather than basal excitatory synaptic transmission and do not change paired-pulse facilitation in mouse hippocampal slices. Brain Res 1560:10–17

Roth BL, Gibbons S, Arunotayanun W, Huang XP, Setola V, Treble R, Iversen L (2013) The ketamine analogue methoxetamine and 3- and 4-methoxy analogues of phencyclidine are high affinity and selective ligands for the glutamate NMDA receptor. PLoS One 8:e59334

Roth BL, Gibbons S, Arunotayanun W, Huang XP, Setola V, Treble R, Iversen L (2018) Correction: the ketamine analogue methoxetamine and 3- and 4-methoxy analogues of phencyclidine are high affinity and selective ligands for the glutamate NMDA receptor. PLoS One 13: e0194984

Salat K, Siwek A, Starowicz G, Librowski T, Nowak G, Drabik U, Gajdosz R, Popik P (2015) Antidepressant-like effects of ketamine, norketamine and dehydronorketamine in forced swim test: role of activity at NMDA receptor. Neuropharmacology 99:301–307

Salomone A, Gazzilli G, Di Corcia D, Gerace E, Vincenti M (2016) Determination of cathinones and other stimulant, psychedelic, and dissociative designer drugs in real hair samples. Anal Bioanal Chem 408:2035–2042

Sanacora G, Smith MA, Pathak S, Su HL, Boeijinga PH, McCarthy DJ, Quirk MC (2014) Lanicemine: a low-trapping NMDA channel blocker produces sustained antidepressant efficacy with minimal psychotomimetic adverse effects. Mol Psychiatry 19:978–985

Seeman P, Ko F, Tallerico T (2005) Dopamine receptor contribution to the action of PCP, LSD and ketamine psychotomimetics. Mol Psychiatry 10:877–883

Sein Anand J, Wiergowski M, Barwina M, Kaletha K (2012) Accidental intoxication with high dose of methoxetamine (MXE) – a case report. Przegl Lek 69:609–610

Shahani R, Stewart RJ (2008) Reply to letter-to-the-editor, Re: Shahani R, Streutker C, Dickson B, et al: Ketamine-associated ulcerative cystitis: a new clinical entity. Urology 69: 810-812, 2007. 71:987

Shahani R, Streutker C, Dickson B, Stewart RJ (2007) Ketamine-associated ulcerative cystitis: a new clinical entity. Urology 69:810–812

Shields JE, Dargan PI, Wood DM, Puchnarewicz M, Davies S, Waring WS (2012) Methoxetamine associated reversible cerebellar toxicity: three cases with analytical confirmation. Clin Toxicol (Phila) 50:438–440

Simmler LD, Buchy D, Chaboz S, Hoener MC, Liechti ME (2016) In vitro characterization of psychoactive substances at rat, mouse, and human trace amine-associated receptor 1. J Pharmacol Exp Ther 357:134–144

Slovenian National Forensic Laboratory (2016) Analytical report. Deschloro-N-ethyl-ketamine (C14H19NO). Slovenian National Forensic Laboratory. https://www.policija.si/apps/nfl_response_web/0_Analytical_Reports_final/deschloro-N-ethyl-ketamine-ID-1607-16-rpt060816.pdf. Accessed 3 Feb 2018

Smith DJ, Azzaro AJ, Zaldivar SB, Palmer S, Lee HS (1981) Properties of the optical isomers and metabolites of ketamine on the high affinity transport and catabolism of monoamines. Neuropharmacology 20:391–396

Stevens CL (1962) Aminoketones and methods for their production. Patent no. US3254124A. Parke Davis, Detroit

Stevens CL (1968) α-Hydroxyimines and aminoketones. Patent No. US3394182A. Parke Davis, Detroit

Stevens CL, Elliott RD, Winch BL, Klundt IL (1962) A new rearrangement of α-aminoketones. J Am Chem Soc 84:2272–2274

Stevens CL, Elliott RD, Winch BL (1963) Aminoketone rearrangements. II. The rearrangement of phenyl α-aminoketones. J Am Chem Soc 85:1464–1470

Stevens CL, Klundt IL, Munk ME, Pillai MD (1965a) Amino ketone rearrangements. IV. Thermal rearrangements of α-amino methyl ketones. J Org Chem 30:2967–2972

Stevens CL, Thuillier A, Daniher FA (1965b) Amino ketone rearrangements. III. The rearrangement of α-hydroxy N-phenylimines. J Org Chem 30:2962–2966

Stevens CL, Ash AB, Thuillier A, Amin JH, Balys A, Dennis WE, Dickerson JP, Glinski RP, Hanson HT, Pillai MD, Stoddard JW (1966a) Amino ketone rearrangements. VI. Synthesis of 2-alkylamino-2-phenylcyclohexanones. J Org Chem 31:2593–2601

Stevens CL, Hanson HT, Taylor KG (1966b) Amino ketone rearrangements. V. A kinetic analysis. J Am Chem Soc 88:2769–2774

Stevens CL, Thuillier A, Taylor KG, Daniher FA, Dickerson JP, Hanson HT, Nielsen NA, Tikotkar NA, Weier RM (1966c) Amino ketone rearrangements. VII. Synthesis of 2-methylamino-2-substituted phenylcyclohexanones. J Org Chem 31:2601–2607

Stevens CL, Cahoon JM, Potts TR, Pillai PM (1972) Epoxyamines. III. Synthesis and reactions of 2-(1-aziridinyl)-2-phenyl-3,3-dimethyloxirane and 2-(1-aziridinyl)-2-phenyl-1-oxaspiro[2.4] heptane. J Org Chem 37:3130–3133

Stewart AT Jr, Hauser CR (1955) Synthesis and reactions of α-dialkylaminobenzyl butyl ethers. Interactions with Grignard reagents to form tertiary amines. J Am Chem Soc 77:1098–1103

Storr TM, Quibell R (2009) Can ketamine prescribed for pain cause damage to the urinary tract? Palliat Med 23:670–672

Striebel JM, Nelson EE, Kalapatapu RK (2017) "Being with a Buddha": a case report of methoxetamine use in a United States veteran with PTSD. Case Rep Psychiatry 2017:2319094

Suzuki K, Nosyreva E, Hunt KW, Kavalali ET, Monteggia LM (2017) Effects of a ketamine metabolite on synaptic NMDAR function. Nature 546:E1–E3

Svenningsson P, Nomikos GG, Greengard P (2004) Response to comment on "Diverse psychotomimetics act through a common signaling pathway". Science 305:180

Tainter ML, Luduena FP, Lackey RW, Neuru EN (1943) Actions of a series of diphenylethylamines. J Pharmacol Exp Ther 77:317–323

Tam SW, Zhang AZ (1988) σ and PCP receptors in human frontal cortex membranes. Eur J Pharmacol 154:343–344

Tan S, Chan WM, Wai MS, Hui LK, Hui VW, James AE, Yeung LY, Yew DT (2011) Ketamine effects on the urogenital system – changes in the urinary bladder and sperm motility. Microsc Res Tech 74:1192–1198

Tang HC, Lam PYH, Liang W (2015) In: Yew DT (ed) Ketamine. Use and abuse. CRC Press, Boca Raton, pp 227–242

Taschwer M, Hofer MG, Schmid MG (2014) Enantioseparation of benzofurys and other novel psychoactive compounds by CE and sulfobutylether β-cyclodextrin as chiral selector added to the BGE. Electrophoresis 35:2793–2799

Thurkauf A, Monn J, Mattson MV, Jacobson AE, Rice KC (1989) Structural and conformational aspects of the binding of aryl-alkyl amines to the phencyclidine binding site. In: Problems of drug dependence, 1989: Proceedings of the 51st annual scientific meeting, the Committee on Problems of Drug Dependence, Inc. NIDA Research Monograph, vol 95. United States Department of Health and Human Services, National Institute on Drug Abuse, Rockville, pp 51–56

Tsai TH, Cha TL, Lin CM, Tsao CW, Tang SH, Chuang FP, Wu ST, Sun GH, Yu DS, Chang SY (2009) Ketamine-associated bladder dysfunction. Int J Urol 16:826–829

Tso MM, Blatchford KL, Callado LF, McLaughlin DP, Stamford JA (2004) Stereoselective effects of ketamine on dopamine, serotonin and noradrenaline release and uptake in rat brain slices. Neurochem Int 44:1–7

Turfus SC, Parkin MC, Cowan DA, Halket JM, Smith NW, Braithwaite RA, Elliot SP, Steventon GB, Kicman AT (2009) Use of human microsomes and deuterated substrates: an alternative approach for the identification of novel metabolites of ketamine by mass spectrometry. Drug Metab Dispos 37:1769–1778

UK S.I. No. 239 (2013) The Misuse of Drugs Act 1971 (Amendment) Order 2013 (Statutory Instrument No. 239). http://www.legislation.gov.uk/uksi/2013/239/pdfs/uksi_20130239_en.pdf. Accessed 27 Mar 2018

Valli A, Lonati D, Locatelli CA, Buscaglia E, Tuccio MD, Papa P (2017) Analytically diagnosed intoxication by 2-methoxphenidine and flubromazepam mimicking an ischemic cerebral disease. Clin Toxicol (Phila) 55:611–612

Van Hout MC, Hearne E (2015) "Word of mouse": indigenous harm reduction and online consumerism of the synthetic compound methoxphenidine. J Psychoactive Drugs 47:30–41

Van Hout MC, Hearne E (2017) New psychoactive substances (NPS) on cryptomarket fora: an exploratory study of characteristics of forum activity between NPS buyers and vendors. Int J Drug Policy 40:102–110

Viceland (2017) Hamilton's pharmacopeia. Season 2. Ketamine; realms and realities. Viceland TV programme. Aired 26 Dec 2017

Vollenweider FX, Leenders KL, Øye I, Hell D, Angst J (1997) Differential psychopathology and patterns of cerebral glucose utilisation produced by (*S*)- and (*R*)-ketamine in healthy volunteers using positron emission tomography (PET). Eur Neuropsychopharmacol 7:25–38

Vutskits L (2018) General anesthetics to treat major depressive disorder: clinical relevance and underlying mechanisms. Anesth Analg 126:208–216

Wallach JV (2014) Structure activity relationship (SAR) studies of arylcyclohexylamines as N-methyl-D-aspartate receptor antagonists. Ph.D. dissertation, University of the Sciences, Philadelphia

Wallach J, Brandt SD (2018) Phencyclidine-based new psychoactive substances. Handb Exp Pharmacol. https://doi.org/10.1007/164_2018_124

Wallach J, Kavanagh PV, McLaughlin G, Morris N, Power JD, Elliott SP, Mercier MS, Lodge D, Morris H, Dempster NM, Brandt SD (2015) Preparation and characterization of the 'research chemical' diphenidine, its pyrrolidine analogue, and their 2,2-diphenylethyl isomers. Drug Test Anal 7:358–367

Wallach J, Kang H, Colestock T, Morris H, Bortolotto ZA, Collingridge GL, Lodge D, Halberstadt AL, Brandt SD, Adejare A (2016) Pharmacological investigations of the dissociative 'legal highs' diphenidine, methoxphenidine and analogues. PLoS One 11:e0157021

Wang S, Li C (1987) Synthesis of anesthetic compound 2-(O-fluorophenyl)-2-methylamino-cyclohexanone hydrochloride (F-ketamine). Acta Sci Nat Univ Pekin 116–119

Wang Q, Wu Q, Wang J, Chen Y, Zhang G, Chen J, Zhao J, Wu P (2017) Ketamine analog methoxetamine induced inflammation and dysfunction of bladder in rats. Int J Mol Sci 18:E117

Ward J, Rhyee S, Plansky J, Boyer E (2011) Methoxetamine: a novel ketamine analog and growing health-care concern. Clin Toxicol (Phila) 49:874–875

Watterson J (2015) Postmortem toxicology of ketamine. In: Yew DT (ed) Ketamine. Use and abuse. CRC Press, Boca Raton, pp 243–248

Weiner AL, Vieira L, McKay CA, Bayer MJ (2000) Ketamine abusers presenting to the emergency department: a case series. J Emerg Med 18:447–451

Weiß JA, Mohr S, Schmid MG (2015) Indirect chiral separation of new recreational drugs by gas chromatography-mass spectrometry using trifluoroacetyl-L-prolyl chloride as chiral derivatization reagent. Chirality 27:211–215

Westphal F, Junge T, Jacobsen-Bauer A, Rösner P (2010) Lefetamin-Derivate: alte Bekannte neu auf dem Drogenmarkt. Toxichem Krimtech 77:46–58

WHO (2014) Methoxetamine. Critical review report. Agenda item 4.22. In: Expert Committee on Drug Dependence thirty-sixth meeting, World Health Organization, Geneva, 16–20 June 2014. http://www.who.int/medicines/areas/quality_safety/4_22_review.pdf. Accessed 3 Feb 2018

WHO (2015) MT-45. Critical review report agenda item 5.1. In: Expert Committee on Drug Dependence thirty-seventh meeting, World Health Organization, Geneva, 16–20 Nov 2015. http://www.who.int/medicines/access/controlled-substances/5.1_MT-45_CRev.pdf. Accessed 27 Mar 2018

Wieber J, Gugler R, Hengstmann JH, Dengler HJ (1975) Pharmacokinetics of ketamine in man. Anaesthesist 24:260–263

Wikstrom M, Thelander G, Dahlgren M, Kronstrand R (2013) An accidental fatal intoxication with methoxetamine. J Anal Toxicol 37:43–46

Wink CS, Meyer GM, Wissenbach DK, Jacobsen-Bauer A, Meyer MR, Maurer HH (2014) Lefetamine-derived designer drugs N-ethyl-1,2-diphenylethylamine (NEDPA) and N-iso-propyl-1,2-diphenylethylamine (NPDPA): metabolism and detectability in rat urine using GC-MS, LC-MS and LC-HR-MS/MS. Drug Test Anal 6:1038–1048

Wink CSD, Meyer GMJ, Meyer MR, Maurer HH (2015) Toxicokinetics of lefetamine and derived diphenylethylamine designer drugs-contribution of human cytochrome P450 isozymes to their main phase I metabolic steps. Toxicol Lett 238:39–44

Wink CS, Michely JA, Jacobsen-Bauer A, Zapp J, Maurer HH (2016) Diphenidine, a new psychoactive substance: metabolic fate elucidated with rat urine and human liver preparations and detectability in urine using GC-MS, LC-MS(n), and LC-HR-MS(n). Drug Test Anal 8:1005–1014

Winstock AR, Lawn W, Deluca P, Borschmann R (2016) Methoxetamine: an early report on the motivations for use, effect profile and prevalence of use in a UK clubbing sample. Drug Alcohol Rev 35:212–217

Wood DM, Davies S, Puchnarewicz M, Johnston A, Dargan PI (2012) Acute toxicity associated with the recreational use of the ketamine derivative methoxetamine. Eur J Clin Pharmacol 68:853–856

Xie L-G, Dixon DJ (2017) Tertiary amine synthesis via reductive coupling of amides with Grignard reagents. Chem Sci 8:7492–7497

Yanagihara Y, Kariya S, Ohtani M, Uchino K, Aoyama T, Yamamura Y, Iga T (2001) Involvement of CYP2B6 in N-demethylation of ketamine in human liver microsomes. Drug Metab Dispos 29:887–890

Yeung LY, Rudd JA, Lam WP, Mak YT, Yew DT (2009) Mice are prone to kidney pathology after prolonged ketamine addiction. Toxicol Lett 191:275–278

Yuizono T, Matsuo S, Nakama M, Kase Y, Fujimura H (1970) Chemico-pharmacological studies on antitussives. X. Pharmacological studies on 1,2-diphenyl-1-tert-aminoethane derivatives. Comparison of the optical isomers of 1,2-diphenyl-1-pyrrolidinoethane. Yakugaku Zasshi 90:24–31

Zanda MT, Fadda P, Chiamulera C, Fratta W, Fattore L (2016) Methoxetamine, a novel psychoactive substance with serious adverse pharmacological effects: a review of case reports and preclinical findings. Behav Pharmacol 27:489–496

Zanda MT, Fadda P, Antinori S, Di Chio M, Fratta W, Chiamulera C, Fattore L (2017) Methoxetamine affects brain processing involved in emotional response in rats. Br J Pharmacol 174:3333–3345

Zanos P, Moaddel R, Morris PJ, Georgiou P, Fischell J, Elmer GI, Alkondon M, Yuan P, Pribut HJ, Singh NS, Dossou KS, Fang Y, Huang XP, Mayo CL, Wainer IW, Albuquerque EX, Thompson SM, Thomas CJ, Zarate CA Jr, Gould TD (2016) NMDAR inhibition-independent antidepressant actions of ketamine metabolites. Nature 533:481–486

Zanos P, Thompson SM, Duman RS, Zarate CA Jr, Gould TD (2018) Convergent mechanisms underlying rapid antidepressant action. CNS Drugs. https://doi.org/10.1007/s40263-40018-40492-x

Zarate CA Jr, Brutsche N, Laje G, Luckenbaugh DA, Venkata SL, Ramamoorthy A, Moaddel R, Wainer IW (2012) Relationship of ketamine's plasma metabolites with response, diagnosis, and side effects in major depression. Biol Psychiatry 72:331–338

Zarate CA Jr, Mathews D, Ibrahim L, Chaves JF, Marquardt C, Ukoh I, Jolkovsky L, Brutsche NE, Smith MA, Luckenbaugh DA (2013) A randomized trial of a low-trapping nonselective N-methyl-D-aspartate channel blocker in major depression. Biol Psychiatry 74:257–264

Zawilska JB (2014) Methoxetamine – a novel recreational drug with potent hallucinogenic properties. Toxicol Lett 230:402–407

Zeilhofer HU, Swandulla D, Geisslinger G, Brune K (1992) Differential effects of ketamine enantiomers on NMDA receptor currents in cultured neurons. Eur J Pharmacol 213:155–158

Zhang DX, Levy WB (1992) Ketamine blocks the induction of LTP at the lateral entorhinal cortex-dentate gyrus synapses. Brain Res 593:124–127

Zhang JC, Li SX, Hashimoto K (2014) *R* (−)-ketamine shows greater potency and longer lasting antidepressant effects than *S* (+)-ketamine. Pharmacol Biochem Behav 116:137–141

Zwartsen A, Verboven AHA, van Kleef R, Wijnolts FMJ, Westerink RHS, Hondebrink L (2017) Measuring inhibition of monoamine reuptake transporters by new psychoactive substances (NPS) in real-time using a high-throughput, fluorescence-based assay. Toxicol In Vitro 45:60–71