

From PCP to MXE: a comprehensive review of the non-medical use of dissociative drugs

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PCP or phencyclidine was discovered in 1956 and soon became a popular street drug. Dissociatives including PCP, ketamine, and dextromethorphan have been used non-medically for their mind-altering effects for over 60 years. Many of these compounds have also been used clinically and in legitimate research. At least 14 derivatives of PCP were sold for non-medical and illicit use from the late 1960s until the 1990s. With the advent of the Internet, the drug market underwent a dramatic evolution. While initially gray-market chemical vendors offering dextromethorphan and ketamine thrived, most recently the market has shifted to legal high and online-based research chemical vendors. Starting with the first dissociative research chemical, 4-MeO-PCP in 2008, the dissociative research chemical market has rapidly evolved and currently comprises at least 12 dissociatives, almost half of which were unknown in the scientific literature prior to their introduction. Several of these, including methoxetamine, have reached widespread use internationally. A historical account of non-medical use of over 30 dissociative compounds was compiled from a diverse collection of sources. The first complete portrait of this underground market is presented along with the relevant legal, technological, and scientific developments which have driven its evolution. Copyright © 2014 John Wiley & Sons, Ltd.

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Introduction

The term 'dissociative anaesthetic' was first used to describe the state of consciousness induced by the uncompetitive *N*-methyl-D-aspartate receptor (NMDAR) antagonist 2-(methylamino)-2-(2-chloro-phenylcyclohexanone or ketamine.^[1] Though most NMDAR antagonists display anaesthetic activity at sufficiently high doses, not all of these agents are used as anaesthetics, thus the broader term 'dissociative' is often employed.

NMDAR's role in the pharmacology of 1-(1-phenylcyclohexyl) piperidine (PCP) (Figure 1), ketamine, and related compounds was first reported in the early 1980s by Lodge *et al.*^[2] NMDAR is a ligand and voltage gated cation channel containing several competitive (binding sites for co-agonists: glycine and glutamate) and non-competitive binding sites (primary amine, zinc, Mg²⁺, PCP). One of three ionotropic glutamate receptors, NMDAR is named after the selective glutamate agonist *N*-methyl-D-aspartate, which is capable of distinguishing NMDAR from other ionotropic glutamate receptors. Uncompetitive NMDAR antagonism, via open channel blockade, is believed to be a primary mode of action underlying the dissociative effects of the compounds discussed. PCP, ketamine, and MK-801 have been shown to bind to a common site (PCP site) inside the ion channel of NMDAR.^[3] The potency with which these compounds induce dissociative effects *in vivo* correlates strongly with NMDAR affinity. A number of structurally diverse antagonists at competitive sites also exhibit dissociative effects in humans.^[4,5] In addition to NMDAR affinity, many dissociatives exhibit affinity for other central nervous system (CNS) receptors including sigma-1, dopamine, opioid and nicotinic and muscarinic acetylcholine receptors which likely modify the activity of the individual compounds.^[6,7]

Despite decades of research and pre-clinical success, therapeutic usage of NMDAR antagonists remains limited. One reason is that NMDAR antagonists exhibit conflicting activity: stimulation and sedation, neuroprotection and neurotoxicity, anti-addictive or reinforcing

addictive activity.^[8] Despite limitations, the number of potential uses of NMDAR antagonists including the treatment of depression, attention deficit hyperactivity disorder (ADHD), neuropathic pain, tinnitus, and neurodegeneration continues to grow.^[1,9] In addition, use of NMDAR antagonists in neuropharmacological research is important in the study of the neural mechanisms in perception and psychosis.^[10,11]

With several dozen clinical trials involving NMDAR antagonists currently recruiting or underway, including use in neurodegenerative diseases, pain, addiction, and more, the history of non-medical human use of these compounds provides clinicians and researchers with a deeper understanding of this complex and fascinating class. In 1980, neuroscientist Edward Domino stated: 'I believe the final chapter of PCP has yet to be written.'^[12] Over 30 years later, the dissociative story is still being written.

This review will focus on uncompetitive NMDAR antagonists with known dissociative activity or their close structural derivatives or so-called analogues. Notably we have chosen not to include selective kappa opioid receptor (KOR) agonists like salvinorin A and mixed NMDAR antagonist/KOR agonists exemplified by the 'psychotomimetic opioids' SKF-10,047 and cyclazocine. Discriminative stimulus studies in animals support the separate classification of selective KOR agonists^[13] and it is our opinion that the qualitative effects of selective KOR agonists and NMDAR antagonists in

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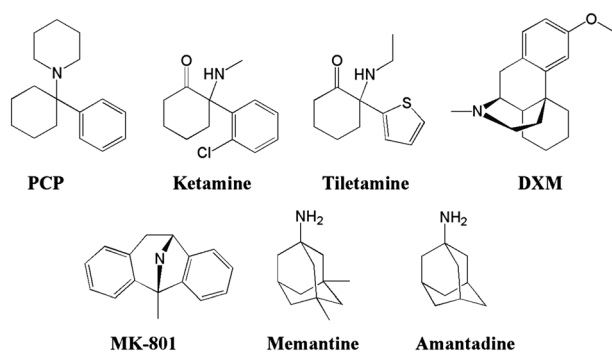


Figure 1. Structures of clinically significant dissociative agents.

humans exhibit distinction and thus may warrant separate classification. Further research into this possibility is certainly appropriate.

The case for mixed NMDAR/KOR ligands like SKF-10,047 and cyclazocine is not as clear. While NMDAR is involved in the discriminative stimulus responses observed with these compounds in animals and likely the dissociative effects in humans, agonist activity at KOR also appears to contribute. This is further supported by cyclazocine derivative ketazocine, a KOR agonist which lacks NMDAR affinity yet induces psychoactive effects including hallucinations in humans at 0.5–1.5 mg/kg.^[14,15] Due to the issue of NMDAR/KOR polypharmacology, these compounds were not included. However it should be noted that some of these compounds have been abused by humans.^[16]

The state that characterizes the dissociative intoxication shows a high degree of dose-dependent variation. Stimulation and, in certain instances, memory improvement occur at low doses while sedation, amnesia, and anaesthesia generally occur at high doses. Perceptual alterations occur in all sensory modalities and include proprioceptive distortions, ataxia, and paresthesias such as tingling, floating sensations, and numbness as well as depersonalization, derealization, and loss of ego boundaries.^[17–19] Visual effects range from distortions, such as impaired depth perception, frequently manifesting as a flattening of the visual field and flickering or strobing to full-scale generative imagery at higher doses.^[17,20,21] Synesthesia has also been reported with PCP, dextromethorphan (DXM), and ketamine.^[11,18,22] Effects on cognition include altered thought patterns with a shift towards greater associative thoughts, ideas of reference, and unusual thought content and in some cases paranoid and grandiose ideology or full-blown delusions.^[17,19] A number of subjective rating scales, including the hallucinogen rating scale (HRS) and the altered states of consciousness rating scale (OAV), have been utilized by researchers to quantify the qualitative effects of ketamine and/or DXM.^[11,23]

Information was reviewed from scholarly and popular sources including scientific, legal, and patent literature, newspapers, online discussion forums, and personal interviews. The Internet was of significant importance to our investigation. Online drug discussion forums like www.bluelight.ru along with websites such as www.erowid.org were used for ethnographic data, as time-stamped records of psychoactive drug usage, platforms for establishing interview contacts, and to obtain reference samples from members for chemical analysis. The anonymity of Internet sources is both an advantage and a limitation of these resources. To limit potential bias, corroboration from multiple sources was sought when possible and in many instances online forum members were privately contacted for additional verification.

Herein we present the first comprehensive review of non-medically used dissociatives with a focus on the historical, synthetic, and pharmacological factors that have driven the development and use of these drugs. Table 1 contains the common abbreviations used and full chemical nomenclature for the compounds discussed.

Arylcyclohexylamines genesis: serendipitous wonder drug

Although PCP is believed to be the first arylcyclohexylamine anaesthetic synthesized, several arylcyclohexylamines were reported before PCP. The primary amine 1-(1-Phenylcyclohexyl)amine (PCA) was initially reported in 1907.^[24] In 1953, a group of Italian chemists led by Stefano Chiavarelli investigated a series of synthetic compounds related to *Erythrina* spp. alkaloids, one of which was *N*-ethyl-1-phenylcyclohexylamine (PCE).^[25] 1-(1-Phenylcyclohexyl)morpholine (PCMo) was described in a German patent filed in 1954 along with several related compounds. Interestingly, the series of compounds including PCMo were described as ‘potent sedatives’ yet their biological activity was not explored further.^[26]

What appears to be the most significant part of the dissociative narrative occurred on 26 March 1956 when the first synthesis of PCP was performed by Victor Maddox of Parke-Davis. Following up an experiment in which 1-(1-ethylcyclohexyl)piperidine was accidentally formed, 1-piperidinocyclohexanecarbonitrile (PCC) was treated with phenylmagnesium bromide and underwent substitution with the grignard reagent rather than the expected addition to the cyano group of PCC.^[27] Though the substitution of alpha-aminonitriles, known as the Bruylants reaction, had been reported in the literature, Maddox was unaware of the reaction at this time.^[27]

Preclinical investigations with PCP proved promising and Parke-Davis quickly filed a patent application detailing PCP’s synthesis and pharmaceutical preparation.^[26] PCP’s pharmacology was first presented at the 1958 meeting of the Federation of American Societies for Experimental Biology followed by publication in 1959.^[28] Human trials began in 1957 at the Detroit Receiving Hospital and replicated the anaesthetic effect observed experimentally in animals. The trials established PCP as a potent general anaesthetic, unique in its absence of respiratory depression. However, adverse effects including agitation, bizarre behaviour, and catatonia were observed in 10 of the 64 patients.^[29] Despite the adverse events, the results were promising enough that PCP was approved by the FDA in 1957 and given the tradename Sernyl. The adverse effects were soon found to be more frequent than anticipated or hoped for and resulted in discontinuation of Sernyl.^[1] As is common in pharmaceutical development, Parke-Davis investigated numerous derivatives of PCP including PCA (CI-401), PCE (CI-400), 1-[1-(thiophen-2-yl)cyclohexyl]piperidine (TCP, CI-421), and *N,N*-diethyl-1-phenylcyclohexylamine (PCDE, CI-482).^[30] PCE and TCP were evaluated in clinical trials at doses of 0.25 to 0.35 mg/kg IV, though they proved to be effective anaesthetics, emergence delirium remained an issue and research was discontinued.^[31,32]

In 1962, research in the laboratory of Calvin L. Stevens, a Parke-Davis consultant, into alpha-hydroxyimine rearrangements produced 2-phenyl-2-(ethylamino)cyclohexan-1-one (2-oxo-PCE). Based on pharmacologic testing in animals this compound was found to be a promising drug lead. Steven’s lab subsequently synthesized a number of related aryl-amino-cyclohexan-2-one-based derivatives including ketamine (sometimes abbreviated CL-369, CI-581). Pharmacological evaluation established ketamine as a short-acting

Table 1. IUPAC chemical nomenclature and common abbreviations	
Abbreviation	IUPAC Nomenclature
PCA	1-Phenylcyclohexan-1-amine
PCP (phencyclidine)	1-(1-Phenylcyclohexyl)piperidine
TCP (tenocyclidine)	1-[1-(Thiophen-2-yl)cyclohexyl]piperidine
TCPy	1-[1-(Thiophen-2-yl)cyclohexyl]pyrrolidine
PCE (eticyclidine, cyclohexamine)	<i>N</i> -Ethyl-1-phenylcyclohexylamine
PCPr (NPPCA)	<i>N</i> -Propyl-1-phenylcyclohexylamine
PCiP (NIPPCA)	1-Phenyl- <i>N</i> -(propan-2-yl)cyclohexan-1-amine
PCPy (rolicyclidine, PHP)	1-(1-Phenylcyclohexyl)pyrrolidine
PCMo (PCM)	1-(1-Phenylcyclohexyl)morpholine
4-Me-PCP	1-[1-(4-Methylphenyl)cyclohexyl]piperidine
4'-Me-PCP	4-Methyl-1-(1-phenylcyclohexyl)piperidine
BnCP	1-(1-Benzylcyclohexyl)piperidine
PCMEA	<i>N</i> -(2-Methoxyethyl)-1-phenylcyclohexan-1-amine
PCMPA	<i>N</i> -(3-Methoxypropyl)-1-phenylcyclohexan-1-amine
PCEEA	<i>N</i> -(2-Ethoxyethyl)-1-phenylcyclohexan-1-amine
4-MeO-PCP (methoxydine)	1-[1-(4-Methoxyphenyl)cyclohexyl]-piperidine
3-MeO-PCP	1-[1-(3-Methoxyphenyl)cyclohexyl]-piperidine
3-MeO-PCPy	1-[1-(3-Methoxyphenyl)cyclohexyl]-pyrrolidine
3-MeO-PCE (methoxieticyclidine)	2-(3-Methoxyphenyl)-2-(ethylamino)cyclohexane
3-MeO-PCPr	2-(3-Methoxyphenyl)-2-(propylamino)cyclohexane
3-HO-PCP	3-[1-(Piperidin-1-yl)cyclohexyl]phenol
3-HO-PCE	3-[1-(Ethylamino)cyclohexyl]phenol
Ketamine	2-(2-Chlorophenyl)-2-(methylamino)cyclohexan-1-one
Tiletamine	2-(Ethylamino)-2-thiophen-2-ylcyclohexan-1-one
Methoxetamine (MXE)	2-(3-Methoxyphenyl)-2-(ethylamino)cyclohexan-1-one
2-MK (2-MeO-ketamine)	2-(2-Methoxyphenyl)-2-(methylamino)cyclohexan-1-one
<i>N</i> -EK (<i>N</i> -ethylorketamine)	2-(2-Chlorophenyl)-2-(ethylamino)cyclohexan-1-one
2-oxo-PCE	2-Phenyl-2-(ethylamino)cyclohexan-1-one
DXM (dextromethorphan)	(4 <i>b</i> 5,8 <i>a</i> <i>R</i> ,9 <i>S</i>)-3-Methoxy-11-methyl-6,7,8 <i>a</i> ,9,10-hexahydro-5 <i>H</i> -9,4 <i>b</i> -(epiminoethano)phenanthrene
(+)-MK-801 (dizocilpine)	[5 <i>R</i> ,10 <i>S</i>]-[+]-5-Methyl-10,11-dihydro-5 <i>H</i> -dibenzo[<i>a,d</i>]cyclohepten-5,10-imine
Memantine	3,5-Dimethyladamantan-1-amine
Amantadine	Adamantan-1-amine
Diphenidine	1-(1,2-Diphenylethyl)piperidine
2-MeO-diphenidine	1-[1-(2-Methoxyphenyl)-2-phenylethyl]piperidine
Lefetamine	(1 <i>R</i>)- <i>N,N</i> -Dimethyl-1,2-diphenylethanamine
Lanicamine	(1 <i>S</i>)-1-Phenyl-2-pyridin-2-ylethanamine
NPS-1506 (deluceimine)	3,3-Bis(3-fluorophenyl)- <i>N</i> -methylpropan-1-amine
2-MDP	3-Amino-2-methyl-1,1-di(phenyl)propan-1-ol
Dexodadrol	2-[(4 <i>R</i>)-2,2-Diphenyl-1,3-dioxolan-4-yl]piperidine
Aptiganel	1-(3-Ethylphenyl)-1-methyl-2-naphthalen-1-yl-guanidine

general anaesthetic. The first human was given ketamine by Edward Domino and Guenter Corrsen on 3 August 1964.^[1] The resultant study on ketamine's effect in 20 prisoner volunteers was published in 1965, establishing ketamine as an effective anaesthetic with a reduced side-effect profile relative to PCP.^[1,33] This same year, Sernyl was voluntarily withdrawn from the market. In 1966, Parke-Davis patented ketamine and related compounds for use as general anaesthetics and the first approved ketamine preparation, Ketalar, was marketed in 1969.^[34]

In addition to veterinary use, ketamine continues to be used in a number of therapeutic areas in humans including general anaesthesia, analgesia, depression, and psychiatric treatment and additional applications are being actively investigated.^[1] However, increasing reports of urotoxicity associated with chronic high-dose ketamine use in medical and illicit users have surfaced.

The urotoxicity of ketamine was reviewed in detail in the recent 10 December 2013 report from the Advisory Council on the Misuse of Drugs (ACMD). Since 2007 there have been hundreds of reported cases of ketamine-associated urotoxicity occurring with both medical and illicit use.^[35]

Non-medical street use: from the laboratory to the street

Non-medical PCP use was first acknowledged in the USA between 1967 and 1968. Although San Francisco and New York were the first cities to report non-medical PCP use, ethnographic studies suggest PCP appeared in Philadelphia, Miami, Seattle, and Chicago around this time.^[36] PCP was once the most common

drug of deception, being sold as, among other things, LSD, mescaline, psilocybin, cocaine, and THC.^[36–38] Between 1971 and 1975 only 8.7% of the PCP and TCP samples detected by the PharmChem Street Drug Program were sold as PCP, TCP, or angel dust. Powder was the most common form detected followed by tablets and lastly impregnated plant matter.^[39] The prevalence of deceptive use may have been responsible for some of the adverse responses initially associated with PCP or, alternatively, the mislabelled drug. Although less common in recent years, PCP remains a drug of deception and has even been encountered in seized ecstasy tablets.^[40]

By 1976, PCP became a media phenomenon with most major newspapers and television networks reporting on PCP use.^[41] Although PCP can induce bizarre psychotomimetic effects, it was often depicted as something out of science fiction. Tales of users with superhuman strength breaking handcuffs, overtaking multiple police officers, and even tearing locked doors off patrol cars were typical.^[22,41] A study on the media's sensationalist portrayals of PCP during this time was undertaken by John P. Morgan and Doreen Kagan^[42] and is further discussed by Philip Jenkins in his book *Synthetic Panics*.^[41] In part facilitated by the media attention, PCP was moved from Schedule III to Schedule II of the Controlled Substances Act (CSA) on 25 January 1978. Use as a veterinary anaesthetic at the time prevented it from entering Schedule I.

Despite reduced media coverage and greater controls, illicit PCP remains common in the USA and Canada, and according to some publications usage is rising in the USA following a slight decline during the late 1980s and 1990s.^[43] For reasons that are not clear, PCP use has remained almost entirely confined to the USA and Canada, with only scattered anecdotal reports describing use in the EU or elsewhere.^[44]

First-generation analogues sold on the traditional street market

The arylcyclohexylamine scaffold contains three distinct regions: an aromatic ring, a geminally substituted cyclohexane ring, and a basic amine function. The first-generation dissociatives distributed on the street market between 1969 and the 1990s, typically involved aryl or amino substitution, and no alteration of the cyclohexane ring. Retaining the cyclohexane ring is a logical decision, as cyclohexane substitution generally decreases NMDAR affinity and PCP-like potency. Though 2-methyl substitution of the cyclohexane ring can increase potency of PCP and TCP, the synthesis produces a diastereomeric mixture that is of reduced potency until resolution of the eutomer is undertaken.^[45,46] Substitution of the aryl and amino regions yields several analogues with equivalent or greater potency than PCP, while at the same time often allowing clandestine chemists to forgo the use of watched chemicals. In other cases, for example ketamine analogues, synthesis is more complex and thus the cyclohexanone analogues have been uncommon.^[47]

All first-generation dissociatives, are simple derivatives of PCP. Although these compounds have not been reported on the street drug market since that era, a number of them have been described by members of online drug forums. In these cases the drugs appear to have been synthesized by the user or obtained directly from the chemist as opposed to being openly sold.

Despite the fact that the first-generation compounds are often called 'designer drugs', in all but one, *N*-(2-ethoxyethyl)-1-phenylcyclohexan-1-amine (PCEEA), they were not designed

by clandestine chemists, but rather developed through legitimate research. Similarly the number of first-generation PCP analogues sold on the non-medical drug market is frequently overestimated in popular and scientific literature. It has been stated that the number is 'over 30'. The true number appears to be closer to 14 (Figure 2) with only three – TCP, PCE, and 1-(1-phenylcyclohexyl) pyrrolidine (PCPy) – becoming prominent with the latter two receiving significant media coverage. This misconception likely stems from misinterpretation of an early publication where mention is made of 30 licit analogues of PCP known scientifically.^[48,49]

The scheduling of PCP may have hastened the appearance of analogues on the illicit market. However, PCE was detected in 1969, prior to the 1970 Controlled Substances Act (CSA) scheduling of PCP, suggesting that the introduction of new compounds can be influenced by factors other than prohibition.^[50] Accordingly, PCP remains the most widely available arylcyclohexylamine and no reports of first-generation PCP analogues appearing on the street were found later than the late 1990s.^[51,52]

1-Piperidinocyclohexanecarbonitrile (PCC)

PCC has occasionally been described as an analogue of PCP, though it is more aptly titled a precursor and contaminant. Illicit PCP samples often contain PCC, in amounts from 0 to 100%.^[38,53,54] PCC also often contributes to the characteristic odour of illicit PCP along with various solvents. PCC has been alleged to be psychoactive^[38,50] and induces rotarod impairment in mice, a property correlating with arylcyclohexylamine potency, with about a fourth of the potency of PCP.^[55] However, PCC is more toxic than PCP^[56] and a report exists of an incorrectly synthesized batch of PCP resulting in severe adverse responses including abdominal cramps, vomiting, and in the worst cases coma and

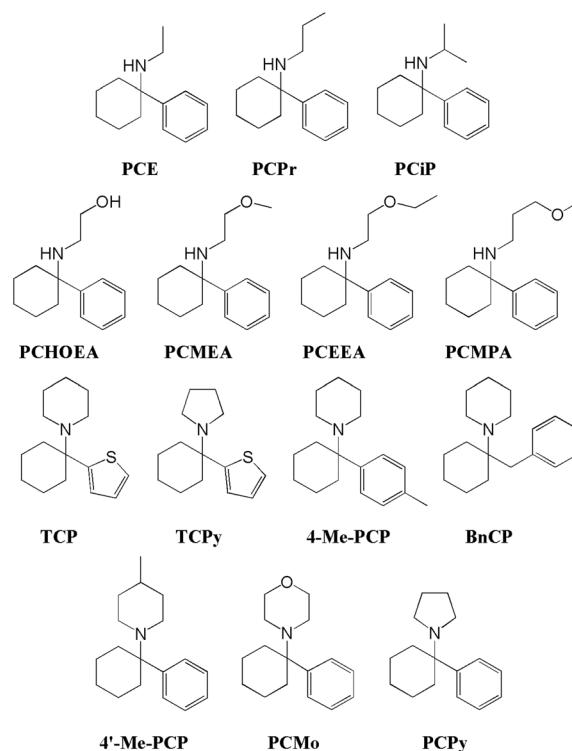


Figure 2. Chemical structures of street analogues of PCP observed from the late 1960s to 1990s.

death.^[57] Handling PCC has reportedly resulted in physical toxicity and psychosis.^[44,53] A portion of the reported symptoms likely result from thermal and metabolic liberation of hydrogen cyanide.^[56,57] PCC and another PCP precursor PCA were placed into Schedule II of the CSA on 17 May 1978 becoming the first drug precursors to be scheduled in the US CSA.^[58] This practice should be discouraged as it has been unsuccessful at limiting illicit production and has the potential to disrupt legitimate research.

1-[1-(Thiophen-2-yl)cyclohexyl]piperidine (TCP)

Substituting PCP's benzene ring for thiophene gives TCP, which was first reported in the patent literature by Parke-Davis in 1960.^[59] TCP was evaluated clinically as an IV anaesthetic in humans by Parke-Davis and displayed similar activity as PCP and PCE.^[32] Although literature from the 1970s generally treat TCP and other analogues as qualitatively interchangeable with PCP, these analogues do display variations in potency and character. Anecdotal reports from the last decade describe TCP as being slightly more potent than PCP by weight, with a longer duration. Some users have described increased hallucinogenic activity.^[60,61] In 1972, TCP was detected in street samples analyzed by the street Drug Identification Program of the LAC-USC Medical Center in LA^[39] and again identified in Hawaii in 1974^[62]; by 1975, TCP and PCP were reported in 25 US states.^[49] Harm reductionists from the *Do It Now Foundation* distributed pamphlets in 1975 warning users about a dangerous trend of PCP misrepresentation, mentioning TCP as being similar in effect but not as prevalent.^[34] A number of TCP samples were detected by the Street Drug Analysis programme (PharmChem,) sold under different names between 1972 and 1975.^[39] Deemed to be without medical value and of high abuse potential TCP was entered into Schedule I of the US CSA on 11 August 1975, making it the first arylcyclohexylamine to be placed into Schedule I.^[63,64] TCP sold as white powder was reported by several authors in 1980.^[57] More recently TCP was synthesized in 2004 and the effects described on the online drug forum *The Hive* as described below.^[61] The related, 1-[1-(thiophen-2-yl)cyclohexyl]pyrrolidine (TCPy) was reportedly analyzed in a 'clandestinely produced sample', although additional details are lacking.^[65] TCPy has PCP like activity in animal models with slightly reduced potency relative to PCP.^[55] TCPy entered Schedule I of the US CSA on 6 July 1989.^[63]

N-Ethyl-1-phenylcyclohexylamine (PCE)

Substituting PCP's piperidine ring for ethylamine gives PCE. Animal behavioural data^[66] human clinical data,^[31] and recent anecdotal reports show PCE to possess equivalent or slightly greater potency than PCP. Supporting this, doses sold in the street market were reportedly smaller than those for PCP.^[50] PCE was first documented in Los Angeles in 1969 and appears to be the first PCP analogue detected.^[50] A 1970 issue of the Drug Enforcement Administration (DEA) journal *DEA Microgram* mentions the detection of a clandestine laboratory presumably synthesizing PCE;^[50] PCE was subsequently encountered in 1971 misrepresented as PCP.^[50] By 1977, PCE's distribution had increased and colourless crystals identified as PCE were detected in Canada.^[67] A 1977 article in the *Detroit Free Press* reported an unconfirmed non-fatal PCE overdose along with

detection of 28 PCE samples by the Michigan State Crime lab and seizure of 300 PCE tablets. Police stated 'hundreds of thousands of tablets' more were on the market.^[68] Within a week of this report, two deaths involving PCE occurred in Wayne County and were described in the toxicological literature.^[69] In June 1978, a clandestine PCE laboratory was detected in Michigan with several pounds of PCE powder, PCE tablets, and tableting equipment.^[70] PCE entered Schedule I of the US CSA on 25 October 1978.^[63] Federal scheduling failed to prevent the drug's distribution and a large number of news reports and legal cases involving PCE between 1978 and 1984 exist including seizures of varying quantities throughout the USA and Canada.^[56,71-75] Most recently 15 ounces of PCE were uncovered in a Pennsylvania clandestine laboratory in 1991.^[76] In all of the cases where data was available PCE was reported as tablets or powder as opposed to a liquid solution or impregnated plant matter, which are common vehicles for smoked PCP. While the reason for this is uncertain, two sources emphasize that clandestinely produced PCE is unpalatable and malodorous compared to related compounds, especially the freebase, which was said to be too caustic for smoking. While pure arylcyclohexylamines generally have little odour, it is possible that an impurity produced during synthesis was responsible.

N-Propyl-1-phenylcyclohexylamine (PCPr) and N-isopropyl-1-phenylcyclohexylamine (PCiP)

Two related compounds involve substitution of the piperidine ring of PCP for *N*-propylamine and *N*-isopropylamine giving PCPr and PCiP, respectively. PCPr has been reported as a PCP analogue by several sources^[55,67] and a 1979 *DEA Microgram* article on PCPr (NPPCA) exists.^[55] PCPr was detected in Germany in the 1990s along with several unusual arylcyclohexylalkoxyamine analogues discussed below leading to its scheduling in Germany.^[52,55] Vaupel *et al.* reported PCiP (NIPPCA) as a recently abused PCP analogue in a 1984 publication citing personal communication with the DEA.^[55,58] At 2.5 mg insufflated PCiP HCl induced dissociative effects with slightly increased potency relative to PCP lasting several hours. The details and extent of PCiP's availability are unknown.

1-(1-Phenylcyclohexyl)pyrrolidine (PCPy)

Substituting PCP's piperidine ring for pyrrolidine gives PCPy or PHP. In the late 1950s, based on the discovery of PCP, investigators at Parke-Davis synthesized and then investigated PCPy for its anaesthetic potential. Consistent with the animal literature PCPy has a similar potency to PCP in humans and is active via smoking, nasal, and oral routes.^[66,77] In addition to classic dissociative effects, PCPy exerts a sedating effect that has been compared to a barbiturate intoxication by some users.^[50] The earliest report of PCPy found was from a sample in Maryland in 1974,^[22] and in 1975 the *DEA Microgram* reported PCPy being sold on leaf material in New Jersey.^[50] A high-profile case reported extensively by national media outlets is the fatal 1977 shooting of publicly intoxicated biochemist Ronald Burkholder by the Los Angeles Police Department (LAPD). PCPy was subsequently detected in Burkholder's post-mortem blood serum.^[78,79] During a 1979 congressional hearing on abuse of dangerous drugs, PCPy was mentioned as an example of the growing issue of PCP analogues. This was based on the fact that 14 reported cases of PCPy were detected in 1977, a rise from earlier years.^[70] PCPy

entered Schedule I of the US CSA on 25 October 1978.^[64] Scheduling did not prevent the distribution of PCPy and as early as June 1979 two individuals were convicted for possession of PCPy in Florida.^[80] The author of a letter to the *New England Journal of Medicine* in 1980 speculated on an increase in PCPy availability in LA around this time, which he called a new drug of abuse. The speculation was based on his observation of a significant rise in PCPy detection in the urine of LA county probationers.^[81] Soon after PCPy was detected in a number of hospitalized patients in Ohio with the intoxication said to resemble that of PCP.^[82,83] Most recently, a clandestine chemist in Boston MA was arrested in 1991 for operating a PCPy laboratory. When arrested, he successfully argued that PCPy was not illegal under MA state law but upon continuing his activity was soon arrested by the DEA in June 1993 and convicted for PCPy manufacture under federal law.^[84]

4-Methyl-1-(1-phenylcyclohexyl)piperidine (4'-Me-PCP) and related analogues

The unusual analogue 4-methyl-1-(1-phenylcyclohexyl)piperidine (4'-Me-PCP), involving substitution of the piperidine ring of PCP with 4-methyl-piperidine, was detected in a street sample from Northern Virginia published in 1981. Analysis found the 4'-Me-PCP HCl was impregnated onto parsley at a concentration of 1.7 % (w/w). Analytical characterization of 4'-Me-PCP was also reported.^[53] 4-Me'-PCP is an unusual choice as it has one-tenth the activity of PCP in a rat drug discrimination assay.^[48,56,88] One online forum report from a www.bluelight.ru member 'adder' described 4'-Me-PCP as active at a third of the potency of PCP.^[85] A related isomer is 1-[1-(4-methylphenyl)cyclohexyl]piperidine (4-Me-PCP), where the 4-methyl substituent is on the benzene ring, and was detected in summer of 1989 in Canada.^[86] At least one report of 4-Me-PCP ingestion exists from www.bluelight.ru member 'adder'. Unfortunately the dose was not given but it was said to be 'disappointing' and 'totally inactive'.^[85] In the same article reporting on 4-Me-PCP, the detection of 1-(1-benzylcyclohexyl)piperidine (PECP, BnCP), in which the benzene ring is replaced by a benzyl substituent, was also described.^[86] 4-Me-PCP and BnCP were established to be of reduced potency in the scientific literature and it is unclear why these were chosen for production or the extent of their availability.^[66,87]

1-(1-Phenylcyclohexyl)morpholine (PCMo)

Replacing the piperidine ring of PCP with a morpholine ring gives PCMo. The commonly used abbreviation currently, PCM, is ambiguous and is inconsistent within current nomenclature. PCMo, specifying the morpholine ring, is more appropriate. To avoid further confusion PCMe will be adopted for *N*-methyl-1-phenylcyclohexylamine. In animal models, PCMo has significantly reduced activity relative to PCP.^[55,77] Posts on *The Hive* exist from the early 2000s and describe PCMo as weaker and of shorter duration than PCP with only minor effects at 150 mg insufflated.^[88,89] In 1977, a laboratory producing PCMo was detected in California, though a DEA chemist stated PCMo had not yet been encountered on the street.^[58] PCMo, PCPy, and TCP were made illegal in California in 1979. PCMo is not presently scheduled by the US CSA.

Arylcyclohexylalkoxyamines

Allen *et al.* report secondary amine 2-aminoethan-1-ol 'analogues have been encountered from clandestine sources' and 2-[(1-phenylcyclohexyl)amino]ethan-1-ol (PCHOEA) was also mentioned on *The Hive* forum in 1999.^[47,60] It is unclear what analogues Allen was referring to; however, several arylcyclohexylalkoxyamines along with PCPr were detected on the illicit market in the late 1990s in Germany including *N*-(3-methoxypropyl)-1-phenylcyclohexan-1-amine (PCMPA), *N*-(2-methoxyethyl)-1-phenylcyclohexan-1-amine (PCMEA), PCEEA.^[52] While PCMPA and PCMEA were reported in a 1961 Parke-Davis patent,^[90] PCEEA was novel at the time of its appearance on the street market. As stated earlier this makes it the only novel first-generation analogue to have been available. A few analytical and metabolic studies of these compounds have been published,^[51,52] but information on their distribution and psychoactivity in humans is limited. PCMEA and PCMPA were stated by a couple members of *The Hive* to be active between 10 and 15 mg with a long duration of action, and PCEEA was said to be active at doses between 15 and 80 mg.^[60,88,91] For convenience, a graphical timeline is presented in Figure 3 showing patterns of usage of 27 dissociative compounds covered in this review.

The Hive: a new online scene

Several online drug forums have fostered detailed discussion of arylcyclohexylamine synthesis and pharmacology. *The Hive* (1997–2004), was an online discussion forum dedicated to the synthesis of psychoactive drugs, and run by author and clandestine MDMA chemist Hobart Huson under the pseudonym STRIKE. Although *The Hive* ceased operation in 2004, many of the threads are archived and available online. Several clandestine arylcyclohexylamine syntheses were discussed including those for PCP, ketamine, and various analogues. In many instances, the synthetic methods were taken directly from or inspired by scientific and patent literature, though novel and theoretical synthetic routes were also discussed. In late 1999, *Hive* member 'John Q. Beagle' ('Beagle') posted an extensive review of arylcyclohexylamine pharmacology and chemistry. Seven synthetic methods for producing PCP and analogues, including PCE (PCC, enamine, imine, Geneste method, Ritter reaction, phenylacetonitrile, and *N*-benzoyl piperidine routes) were reviewed. Arylcyclohexylamine SAR, pharmacology, and previously unpublished human bioassays were also discussed. Foreshadowing, if not influencing the future research chemical (RC) market, several arylcyclohexylamines mentioned later became important RC dissociatives including 3-[1-(piperidin-1-yl)cyclohexyl]phenol (3-HO-PCP), 1-[1-(4-methoxyphenyl)cyclohexyl]-piperidine (4-MeO-PCP), and 1-[1-(3-methoxyphenyl)cyclohexyl]-piperidine (3-MeO-PCP). Other relevant threads posted on *The Hive* include detailed, and sometimes photographically illustrated, synthetic reports for 4-MeO-PCP (Bruylants PCC route),^[92] PCDE (enamine route),^[93] PCMo (enamine route),^[89] TCP (enamine route),^[61] and *N*-propyl-1-(thiophen-2-yl)cyclohexan-1-amine (TCPPr) (imine route).^[94] Synthetic schemes illustrating the synthesis of PCP, PCPy, and PCE are shown for the Geneste, Bruylants, enamine, and imine route in Figure 4.

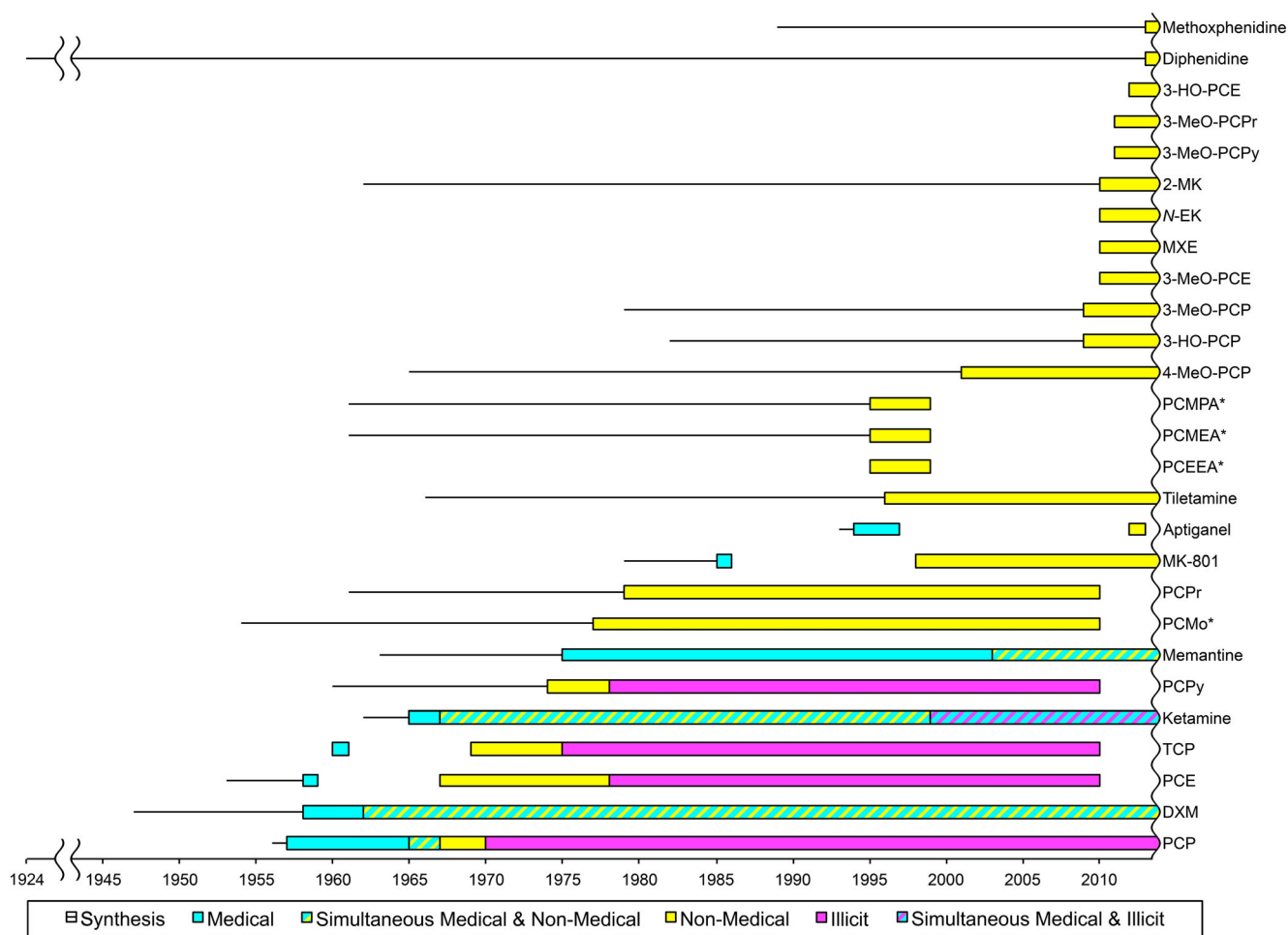


Figure 3. Graphical timeline of twenty-seven dissociatives showing history of first documented synthesis, non-medical use, medical use, simultaneous medical and non-medical use, illicit (illegal) use, simultaneous illicit and non-medical use. Black horizontal line length corresponds to time between first synthesis and subsequent event. * indicates tentative data due to limited number of available sources.

Non-medical ketamine

Unlike PCP, ketamine has global popularity.^[44] The ketamine user-base and distribution networks differ from those of contemporary PCP.^[95,96] While PCP has become largely a street drug, ketamine is popular among rave and club-goers as well as psychonauts, individuals who use altered states to explore perceptual and spiritual phenomena.^[8] Illicit ketamine is often encountered as a white crystalline powder or pharmaceutically packaged injectable solution and is generally insufflated, injected, or less commonly consumed orally. Ketamine has been sold as a drug of deception as ecstasy in the USA and in the EU.^[8,44] Clandestine synthesis of ketamine in the USA has not been reported, though it may occur in rare instances; this is likely due to ketamine's relatively low potency and technically demanding synthesis (Scheme 2).^[47]

Interviews by Karl Jansen suggest non-medical ketamine was available as early as 1967–1968 and was 'being spread by rogue "medicinal chemists" from Michigan to the Florida coast offered as "mean green" and "rockmesc"'.^[8] In 1971, the year following FDA approval on 19 February 1970, non-medical use of ketamine solutions was noted in California and the first scientific report on the use of ketamine for 'psychedelic effects' was published in a 1971 letter to the *New England Journal of Medicine*.^[97,98] Unlike PCP, ketamine use as a psychoactive substance appears to have

been rare during this time. In the late 1970s, ketamine began to attract more attention, including mention in a popular counter-culture comic *Fabulous Furry Freak Brothers* in 1976 and *High Times* magazine in 1978. The 1979 Street Drug Analysis Results reported detecting ketamine in drug samples.^[39] In 1978, neuropharmacologist Ronald Siegel published a study on recreational users of PCP and ketamine^[97] and the psychoactive effects were further popularized with two 1978 publications: *Journeys into the Bright World*^[99] by author Marcia Moore and Howard Alltounian, and *The Scientist* by neuroscientist John Lilly.^[100] These authors described unique dissociative landscapes including vivid descriptions of the immersive visual hallucinations and perceived altered realities. Despite FDA concern about non-medical use of ketamine, ketamine use remained uncommon^[101] and the DEA turned down a 1981 request from the US Department of Health and Services (DHHS) for scheduling because 'the incidence of actual abuse was not sufficient to sustain the scheduling action'.^[102] By 1995, this changed and the office of the US Director of the Office of National Drug Control Policy added ketamine to its 'emerging drugs list'^[103]; in 1999, ketamine was placed into Schedule III of the US CSA, allowing continued medical use.

Prior to scheduling, ketamine was available from chemical supply companies. The Internet and the international postal system greatly facilitated ketamine distribution. Mail-order ketamine was

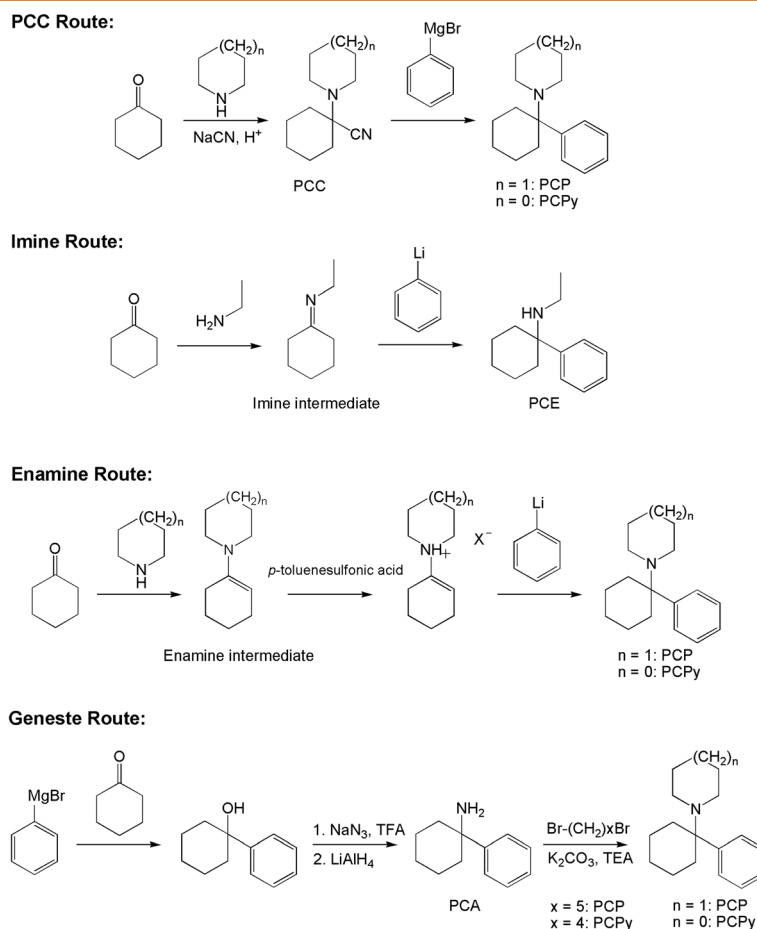


Figure 4. Four common synthetic routes for the synthesis of arylcyclohexamines; PCC, Imine, Enamine, and Geneste routes. By substituting intermediates in key steps of these reactions a variety of PCP analogues and derivatives can be produced.

acknowledged online as early as 1998 in *The DXM Zine*, an online magazine dedicated to the dissociative DXM, as well as discussions on alt.drugs newsgroups.^[104,105] Likewise ketamine continued to be available through several chemical supply vendors, including The Science Alliance run by Hobart Huson of *The Hive* who imported and resold ketamine from Hong Kong, China.

Scheduling in the US did not appear to limit the international availability of ketamine and various online drug forums contain posts describing how bulk ketamine was obtained via Internet sources. Diversion of pharmaceutical preparations remains common and in 2002 several busts of US-based suppliers obtaining vials of ketamine from labs in Mexico occurred.^[96]

During the early 2000s, ketamine had also become popular in the UK, particularly on the rave dance scene and began to receive attention through media outlets including the London magazine *Time Out*.^[8] In the UK, ketamine was classified as a Class C drug following an amendment of the 1971 Misuse of Drugs Act in 2005. A recent report from the Advisory Council on the Misuse of Drugs (ACMD) reported on a recent increase in ketamine misuse in the UK. A number of topics related to ketamine are reviewed including chemistry, pharmacology, misuse, and medical and social harms. In addition, a recommendation is made that ketamine be reclassified to a Class B drug on the basis of increased evidence of physical harm specifically related to bladder toxicity.^[35] It is worth mentioning that between 2000 and 2007 physicians in Hong Kong treated a series of ten ketamine abusers who presented with irritative bladder symptoms including

frequent, urgent urination and haematuria. Examination revealed a significant reduction in bladder capacity and abnormal liver function in all patients, with most displaying bilateral hydronephrosis.^[106] The publication of these case reports in 2007 is the first known instance of ketamine-associated bladder dysfunction, despite ketamine having over 40 years of use. However reports of adverse effects including 'K pains', described as stomach or abdominal pains, by heavy users of ketamine were mentioned by Jansen, though at the time he speculated these pains could be psychosomatic.^[8] *In vitro* cell culture studies on human urothelial cells show that ketamine and the metabolite norketamine exhibit dose-dependent cytotoxic effects. However it is unclear if NMDAR is necessarily involved in this urotoxicity as (+)-MK-801 failed to induce these effects. Interestingly however, (+)-MK-801 potentiated ketamine's toxicity.^[107]

Today illicit ketamine is believed to originate from diverted pharmaceutical production or illicit production from producer countries such as Mexico, European states, India, and China.^[44,108,109] These countries have large pharmaceutical production industries and access to necessary equipment and precursors with less regulatory oversight than the USA and the UK. The Internet and mail system remain key components of the trade. The recently dismantled SilkRoad website, an Internet-based drug distribution hub, also hosted numerous ketamine vendors. In recent years, some legislative attempts to disrupt the trade have been made. China reported seizing two illicit laboratories in 2009 in possession of the ketamine intermediate hydroxylamine hydrochloride, and in 2010, China

announced implementation of greater controls on the manufacture of this intermediate.^[44] India has also implemented greater controls in recent years.^[110] These controls have had little impact on the global ketamine trade.

2-(Ethylamino)-2-thiophen-2-ylcyclohexan-1-one (tiletamine) was developed by Parke-Davis for veterinary anaesthetic use as an alternative to ketamine.^[111] Parke-Davis patented tiletamine in 1966. Tiletamine's pharmacology was published in 1970.^[111,112] Telazol, a tiletamine and zolazepam preparation, was placed into Schedule III of the CSA in 1987.^[63] Between 1999 and 2001, reports of veterinary tiletamine/zolazepam abuse appeared in the USA and in South Korea, including two fatal overdoses.^[113,114] Several www.erowid.org experience reports involving tiletamine exist. Although more potent than ketamine, many users reported non-euphoric effects or described tiletamine as unpleasant relative to ketamine.^[115,116] A limited number of posts on online drug forums such as on www.bluelight.ru on tiletamine usage also exist and describe similar effects. Although several RC vendors have listed tiletamine at various times, evidence suggests it has never been widely available or used.

Dextromethorphan (DXM): origins

Morphinan-based dissociative DXM is the *d*-isomer of the opioid analgesic methorphan. The methorphan synthesis was first described in a US patent filed by pharmaceutical company Hoffmann-La Roche in 1947.^[117] Synthesis and resolution of DXM was subsequently patented in 1952. DXM was approved by the FDA in 1958 and introduced as a non-prescription replacement for codeine-based antitussives under the brand name Romilar.^[118] DXM lacks opioid activity but was shown to be a moderate-low potency NMDAR antagonist.^[119,120] The dissociative and active O-demethylated metabolite dextrorphan (DXO) has even greater NMDAR affinity.^[119] DXO has been evaluated clinically in humans and was found to induce dissociative effects including hallucinations^[121] and may play a role in some the psychoactivity of DXM. DXM was specifically excluded from the US 1970 CSA (as it was an isomer of Schedule II drug levomethorphan and thus would have been scheduled as a stereoisomer unless specifically exempt).

DXM is the subject of numerous books, television specials, websites, and magazine and newspaper articles, and has earned an almost religious significance among some proponents.^[122] A recent clinical study on the psychoactive effects of DXM supports the possibility of DXM-induced spiritual effects and mystical-type experiences.^[11]

DXM appears to be the first synthetic dissociative used for non-medical psychoactive effects, starting in the early 1960s with several members of the Beatnik generation reported to have ingested the compound.^[123] Some of the earliest scientific literature published in the early 1960s on DXM intoxication come from Europe and Australia.^[124–126] The psychoactivity of DXM containing cough syrup was noted in a 1968 US 'drug abuse' publication under the heading 'other drugs with abuse potential'. The article stated DXM cough syrups produce 'a central effect' in large doses. Interestingly the altered state was partially attributed to the antihistamine and decongestant co-additives.^[127] A controlled study on dextromethorphan's psychoactive effects in humans was published in 1971 and revealed that DXM has prominent psychotomimetic effects at doses 6–10 times greater than therapeutic antitussive doses.^[128] Concerns about recreational use led to removal of Romilar tablets from the US market in

1973, but DXM-containing cough syrups remained available due to a perceived lower risk of abuse.^[117,129]

In the USA, adolescent abuse of DXM-containing products was reported by at least 14 states in the late 1980s. In Utah, this abuse led to pharmacies voluntarily moving DXM containing products behind the counter.^[124] In addition to the USA, non-medical DXM use occurred in Europe and the alleged first two fatal intoxications occurred in Sweden in the 1980s.^[130]

Since the mid-1990s, the Internet has become the major conduit for transmission of information on DXM. In 1994, researcher William E. White published an exhaustively referenced review of DXM psychopharmacology, history, and toxicity on the Internet discussion system Usenet. Special reference was given to reducing harm from recreational use of cough syrups containing additional active ingredients.^[131]

Starting in 1994, Usenet became an active online forum for discussion of DXM use and DXM cough syrup extraction techniques. Usenet posts suggest that pure DXM HBr powder was available from gray-market chemical vendors as early as the autumn of 1996. In February 1997, the gray-market chemical supply company Chemical Resale of Santa Barbara advertised prices for pure DXM HBr on Usenet. DXM may have been available via mail-order services earlier but to the best of our knowledge the above represent the first instances of pure DXM being openly sold online. The first issue of the online magazine *The DXM Zine*, was published in November 1997. An article on DXM extraction from cough medicines was included along with a listing of powder DXM vendors.^[105] The subsequent December 1997 issue includes user reports on DXM HBr powder and bulk DXM HBr prices as low as a dollar a gram.^[104] A 1998 letter to *Annals of Emergency Medicine* detailed two case reports involving abuse of DXM powder.^[132] By the late 1990s and early 2000s DXM use had become widespread. The founders of www.erowid.org publicly commented that they were forced to reject the majority of DXM experience reports due to an extraordinary large volume of submissions.

Following the DEA's 2004 *Operation Web Tryp*, a large-scale gray-market drug bust, DXM powder suppliers became less abundant and visible. However DXM was not scheduled and DXM HBr powder is still offered on the RC market and in bulk from Chinese, Indian, and European retailers. In the USA, DXM use remains common especially among adolescents^[133] and DXM cough medicines remain readily available over the counter. Some states have prohibited sale of DXM-containing products to minors^[134] and in recent years there have been discussions placing increased restrictions on the sale of DXM.^[135] Finally like other dissociatives DXM has been used as a drug of deception and has been reported to have been sold as ecstasy, heroin, and ketamine.^[134]

MK-801

The dibenzocycloheptene MK-801 was first synthesized in 1979 by Marcia Christy and Paul Anderson at Merck Pharmaceuticals. Pharmacological tests in rodents established MK-801 to have sympathomimetic activity and extraordinarily potent anticonvulsant activity.^[136,137] Beginning in 1985, a number of small open-label clinical investigations of MK-801 were undertaken. Areas investigated included use as a supplemental therapy for refractory epilepsy, anxiety, depression, and adult attention deficit disorder (ADD).^[136] Results were mixed and further clinical research was halted due to inconsistent efficacy, behavioural side effects, and observed neurotoxicity in rats (described below).^[9]

Due to its mixed stimulant and depressant effects, MK-801 was initially thought by some clinicians to represent a novel pharmacological class. However, in 1986, MK-801's action as a high potency uncompetitive NMDAR antagonist was discovered.^[138] Despite the lack of clinical use, MK-801 has become one of the most common glutamatergic ligands in neuropharmacological research.^[139]

Non-medical MK-801 ingestion was traced back to a 1998 Usenet post describing an intravenously administered 100 µg dose that compared favourably to PCP and ketamine.^[140] In 2002, a MK-801-associated fatality was reported implicating a 25-mg dose co-ingested with ethanol, diazepam, and temazepam. The decedent's (+)-MK-801 maleate had been obtained from a mail-order biochemical supplier.^[141] Consistent with this, online forum posts and interviews suggest legitimate chemical suppliers are the predominant means by which many users acquired MK-801. However, at least one RC source, New-Jersey-based Jmar Chemical, offered (+)-MK-801 maleate from 2003 to 2004. In May 2004, a www.bluelight.ru member posted repeatedly about his experiences injecting (+)-MK-801 IM obtained from Jmar Chemical, suggesting the drug was dysphoric and gave him 'telepathic abilities'.^[142]

Non-medical MK-801 use is very limited and less than a dozen user reports have appeared online as reports on www.erowid.org or on drug forum posts for example on the private forum www.dextroverse.org since 2004.^[142,143] These reports indicate MK-801 has remained unobtainable or undesirable for prospective users. Though these reports differ in their qualitative assessment, there is agreement that MK-801 is a potent dissociative via oral and parenteral routes with a long duration, often in excess of 24 h. Classic dissociative and stimulant activity are reported at doses ranging from 250 µg to 3.5 mg orally, with doses over 2 mg often producing immersive closed-eye visualizations that are sometimes accompanied by external auditory hallucinations, sensed presence or entity hallucinations, speech disfluency, and anterograde amnesia.^[142,143]

In 1989, Olney *et al.* reported an apparent neurotoxic effect occurring with (+)-MK-801, PCP, tiletamine, and ketamine in adult female Sprague Dawley rats.^[144] Following subcutaneous injection, morphological changes were observed using light and electron microscopy and included formation of vacuoles in the cytoplasm of varying sizes. Neurons affected were medium to large sized neurons in layers III and IV of the posterior cingulate and retrosplenial cortices. The effect was sex, age and dose dependent. While the lesions generally disappeared over time, high doses of (+)-MK-801 and PCP induced necrosis in susceptible cells. Potency of the toxicity correlated with NMDAR affinity^[144] and competitive NMDAR antagonists also induce these lesions.^[145] However, the role of NMDAR in lesion induction is unknown, as some NMDAR antagonists do not appear to induce lesions to the same degree, including gacyclidine^[146] and remacemide.^[147]

While the etiology is unknown, compromised 'energy metabolism' has been speculated to play a role. Interestingly lesions are prevented by co-administration of a number of pharmacological agents including 5-HT_{2a} agonists, anticholinergics, and barbiturates.^[148,149] Karl Jansen discussed the matter in his book *Ketamine: Dreams and Realities*, presenting results from several unpublished studies which found ketamine (10 mg/kg) and MK-801 did not produce vacuoles in monkeys.^[8] Unfortunately specific details of these studies are lacking and more work is needed to determine the relevance of these lesions to humans.

Adamantines

3,5-Dimethyladamantan-1-amine (memantine) and adamantan-1-amine (amantadine) (Figure 1) are both adamantan-amine based uncompetitive NMDAR antagonists.^[150] These drugs have important therapeutic uses in Alzheimer's and Parkinson's Disease and are generally considered well-tolerated.^[151] Memantine substitutes for PCP or (+)-MK-801 in rats and monkey drug discrimination paradigms. Full substitution occurred at relatively high doses that generally cause a reduction in response rate. Likewise intravenous memantine and amantadine serve as a positive reinforcers in rhesus monkeys trained to self-administer PCP.^[151] Isolated reports have been posted to websites such as www.erowid.org and the counter-culture magazine *The Entheogen Review* of human use at supra-therapeutic doses to induce dissociative effects, with users describing 100 mg oral doses of memantine and oral doses of amantadine in excess of 2 g.^[152-154] Results from clinical studies support these reports of dissociative activity.^[155,156] While many users described the effects as positive, neither compound has been widely used as a dissociative likely due to the long duration of action (over 40 h). Factors that may limit abuse-liability are discussed in greater detail in the future perspectives section. Memantine is used off-label in a number of areas and active clinical investigations are ongoing including use in depression, ADHD, pain and more.^[157] Therapeutic doses (~10 mg) of memantine induced a mild altered state with cognitive stimulation and altered thought patterns with some parallels to low dose arylcyclohexylamines.

Anisylcyclohexylamines

A 1965 article published by Maddox^[158] described the synthesis of two of the three isomeric 1-anisylcyclohexylpiperidines 1-[1-(2-methoxyphenyl)cyclohexyl]-piperidine (2-MeO-PCP) and 4-MeO-PCP. Preparation of 3-MeO-PCP was described later in 1979 by Geneste *et al.*^[159] NMDAR binding of the anisylcyclohexylamine isomers has been characterized, with 3-MeO-PCP displaying greatest NMDAR affinity followed by 2-MeO-PCP.^[7,160] Psychoactive effects of 3-MeO-PCP and 4-MeO-PCP in humans (Figure 5) were first described by *Hive* member 'hms_beagle' around 1999 in his review 'Synthesis and Effects of PCP Analogs A Review by John Q Beagle'. Beagle describes 3-MeO-PCP as 'producing effects in man that are extremely similar to PCP in potency and quality'. Beagle went on acknowledging the potential of several additional anisylcyclohexylamines including three future RC dissociatives 2-(3-methoxyphenyl)-2-(ethylamino)cyclohexane (3-MeO-PCE) and the novel 1-[1-(3-methoxyphenyl)cyclohexyl]-pyrrolidine (3-MeO-PCPy) and 2-(3-methoxyphenyl)-2-(propylamino)cyclohexane (3-MeO-PCPr).^[60] Beagle also described the first documented clandestine synthesis of an anisylcyclohexylamine, 4-MeO-PCP, which was posted to *The Hive* on 11 September 2001. Executed under 'primitive' conditions in a residential laboratory, Beagle states that the 4-MeO-PCP produced was active in humans with a reduced potency ('rough estimate' of 70%) and reduced duration relative to PCP.^[92]

Beagle's 4-MeO-PCP report remained a subject of intermittent discussion on online forums but no further bioassays were conducted. *The Hive* was taken offline in 2004, disrupting Internet discussion of clandestine chemistry. At the time the burgeoning Internet trade of psychoactive RCs was largely focused on serotonergic tryptamines and phenethylamines, and the only dissociatives

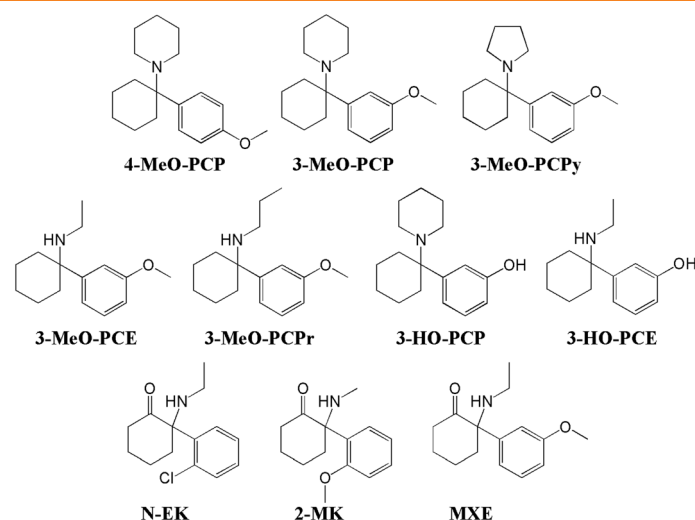


Figure 5. Research chemical anisylaryl-cyclohexylamines and aryl-amino-cyclohexan-2-ones.

sold online were compounds with pre-established medical or scientific utility such as DXM, ketamine, and to a lesser extent MK-801. Horror stories of the previous 40 years appear to have stigmatized PCP among many drug users and this stigmatization was reinforced by influential members on drug forums like www.bluelight.ru who cautioned against the disastrous behavioural toxicity that could result from the introduction of gray-market PCP derivatives.

This changed in December 2008 when UK-based vendor www.chembay.co.uk began offering 4-MeO-PCP for £75.00 per gram. Reports of use on multiple drug forums such as www.bluelight.ru and www.drugs-forum.com followed but contrasted Beagle's initial description when users found 4-MeO-PCP to be at least an order of magnitude less potent than PCP with comparable or longer duration. In addition, reports indicated varying potency between batches and vendors, with some users requiring several hundred milligrams to achieve threshold effects. A possible explanation is documented variations in purity of analyzed samples, with one sample predominantly containing the precursor PCC, the same intermediate that frequently contaminates illicit PCP samples. Regarding this particular analysis, the analysis company, www.ecstasydata.org, stated: 'This is probably the dirtiest Research Chemical we've ever seen, in 15 years of watching analyses of gray market and black market chemicals.'^[161] Despite the issue of variability 4-MeO-PCP was overall positively received by users. By 2010, a second vendor of 4-MeO-PCP had emerged in Denmark called www.RCstandards.com and availability gradually increased. A sample of material from www.RCstandards.com obtained in October 2010 was also analyzed by www.ecstasydata.org by gas chromatography–mass spectrometry (GC-MS) and was predominantly 4-MeO-PCP.^[161] 4-MeO-PCP was first reported to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) on 11 January 2011 in Finland. The first adverse response to 4-MeO-PCP involving a 4-MeO-PCP-polydrug intoxication was reported to the EMCDDA in Norway in August 2011.^[162] The DEA published a 2011 *Microgram* article with GC-MS and nuclear magnetic resonance (NMR) data and acknowledged 4-MeO-PCP as an RC.^[163]

The introduction of 4-MeO-PCP was a watershed moment for gray-market dissociatives and marked an important bridging of classic clandestine chemistry with the new Internet-mediated drug trade. For the first time a dissociative anaesthetic without pre-established medical or scientific utility was being sold for the purpose of non-

medical use, and the perceived lack of significant adverse reactions reassured vendors and users alike that PCP derivatives could be circulated as RCs. Yet, in the opinion of many users, 4-MeO-PCP's low potency and long duration left room for improvement.

In April 2009, Swiss chemist and www.bluelight.ru member 'hugo24' first reported positively on the psychoactive effects of 3-MeO-PCP in a number of posts.^[164] 3-MeO-PCP is active via oral and parental routes and induces dissociative activity beginning at 5 mg, although many users ingest significantly higher doses. The effects are often described as more euphoric and mentally clearer than many related compounds. Shortly after hugo24's initial reports, a number of other prominent www.bluelight.ru members confirmed these claims reporting enthusiastically on the psychoactive effects of 3-MeO-PCP. These members had initiated a collaborative research effort where international www.bluelight.ru members participated in designing, synthesizing and characterizing various arylcyclohexylamines including 3-MeO-PCP, 3-MeO-PCE, 2-oxo-PCE, and several novel compounds including 3-MeO-PCPy, 3-MeO-PCPr and 2-(3-methoxyphenyl)-2-(ethylamino)cyclohexan-1-one (methoxetamine, MXE). A significant feature of this project was the apparent interest in novel compounds for psychotherapy and treatment of phantom limb pain ('fastandbulbous' pers. comm.).

2-(3-Methoxyphenyl)-2-(ethylamino)cyclohexan-1-one (methoxetamine, MXE): origins

The first of the bluelight research group's compounds to become widely available appears to be MXE. Although theoretical properties of 2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone were initially described in a 2006 www.bluelight.ru thread on novel psychoactive drugs by member fastandbulbous, it was not synthesized until a few years later. After a series of positive self experiments with a variety of anisylcyclohexylamines, fastandbulbous suggested the structure of MXE to collaborator hugo24, who synthesized the compound. fastandbulbous speculated that the 3-MeO- substitution would provide an opioid analgesic effect, while substituting the *N*-methyl to an *N*-ethyl would increase duration and potency, while the 2-keto group would allow the compound to retain the relative safety and character of ketamine. The first public report on MXE's qualitative effects was posted by

fastandbulbous on www.bluelight.ru on 13 May 2010. Titled 'First Time: Heaven on Earth', the post describes a 25-mg IM injection and praised MXE, placing emphasis on the resultant 'state of bliss'. The emphasis on opioid activity is an example of folk pharmacology and is based on the fact that 3-HO-PCP has high affinity for the μ -opioid receptor (MOR).^[165,166] Despite the intent, 3-MeO-PCP and MXE do not appear to have MOR affinity below 10,000 nM.^[7] Still this myth is commonly acknowledged as fact on online drug forums and has even appeared in recent peer-reviewed literature.^[167] Notably, phase I metabolic demethylation of MXE does produce a 3-hydroxylated metabolite, which may exhibit MOR activity however this remains to be established.^[168,169]

Immediately following the report, fastandbulbous received several inquiries regarding MXE, including one from the proprietor of a London-based RC vendor who was interested in making MXE commercially available (fastandbulbous, pers. comm.). On 10 September 2010, three months after the initial report, www.buyresearchchemicals.co.uk (BRC) announced its intent to market MXE as 'methoxetamine', a name fastandbulbous originally coined as a contraction of methoxy-ketamine.

On 14 September 2010, the first 15 free 50-mg samples of MXE were offered by BRC to UK customers. Within days, a series of user reports appeared on www.bluelight.ru and at least one vendor, www.blueagricultural.co.uk, exploited demand by selling caffeine powder misrepresented as MXE. An initial misidentification of this sample as *N*-methyl-1-(thiophen-2-yl)cyclohexanamine (TCM or TCMe) based on GC-MS appeared on www.bluelight.ru. There was great interest in MXE, which initially sold for £80.00 a gram from BRC, a particularly high price relative to illicit ketamine in the UK, which was reportedly as inexpensive as £10.00 per gram. An unpublished analysis of an early BRC sample was consistent with high purity racemic MXE HCl based on optical rotation, high performance liquid chromatography (HPLC), ¹³C and ¹H NMR and C, H, N elemental analysis. A 2012 *DEA Microgram* article reported the analytical characterization of MXE (MS, ¹H and ¹³C NMR and FTIR)^[170] and several RC samples of MXE have been analyzed.^[171]

MXE was immediate *cause célèbre* among drug forum members and Internet discussion continued at rapid pace. The first MXE overdose was reported on 21 October 2010 by the UK-based *Harlow Star* newspaper. An emotionally unstable woman attempted suicide by reportedly consuming 80–100 mg MXE which was suggested to induce a psychosis that warranted medical intervention. Reporters looking to identify the compound, which had not yet been described in media circles, came upon a discussion of TCM (TCMe) and MXE online, and arbitrarily used the name Methoxythyl.^[172] A subsequent unconfirmed overdose described the fatal overdose of a Swedish man who injected 400 mg of the serotonin releaser RC MDAI (5,6-methylenedioxy-2-aminoindane) and 100 mg of MXE, dampening some initial enthusiasm about the safety of MXE among users.^[167] MXE was first reported to the EMCDDA on 9 November 2010 by the UK.^[173] The first publicized and detailed discussion of MXE's origins and psychoactive effects were published as an interview with MXE's inventor fastandbulbous in the February 2011 issue of *Vice* magazine.^[174]

The first reference to MXE in the scientific literature appeared as an August 2011 letter to *Clinical Toxicology* describing a single adverse response from an intravenous user.^[175] Attesting to MXE's growing popularity at this time, the EMCDDA identified 58 websites in July 2011 offering MXE; although it is uncertain how many of these websites were legitimate vendors the large number clearly attests to MXE's increasing popularity.^[176] In addition to powder, MXE was sold online and in bricks-and-mortar shops in foil

envelopes of 35 mg 'pellets'.^[177] Additionally, packets of MXE powder labeled 'Special K', a common slang term used for ketamine, were available. These are the first instances of such branding being used with an RC dissociative we have encountered.^[178]

Scientific publications on MXE intoxication and fatalities soon appeared with increasing frequency.^[179–181] While designed in part to have a decreased potential for urotoxicity due to an increased potency (fastandbulbous, pers. comm.) preliminary research from animal studies suggest MXE (30 mg/kg for three months) can cause bladder and kidney toxicity in mice.^[182] Reports of urotoxicity with MXE in humans have not been documented. As the urotoxicity appears to be dose dependent, it is possible if lower doses are used that MXE may have lower potential for urotoxicity. On 5 April 2012, MXE was placed under temporary class drug control prohibiting import and sale in the UK for 12 months. Upon request from the UK, the EMCDDA began collecting available information on MXE. The subsequent response was used by the ACMD in its 18 October 2012 report to suggest a Class B scheduling status. The ACMD also suggested the implementation of a generic definition to control arylcyclohexylamines.^[162] On 26 February 2013, MXE along with derivatives of 1-phenylcyclohexylamine became Class B drugs in the UK effectively banning all existing RC dissociatives available at the time and many additional arylcyclohexylamines.^[183] This report also described the receptor binding profile of MXE and two additional RC dissociatives 3-MeO-PCP and 3-MeO-PCE, showing them to have significant affinity for the PCP site of NMDAR.^[184] This pharmacological work was later published in more detail.^[7]

Shortly after the introduction of MXE, BRC continued to offer novel anisylcyclohexylamines from the www.bluelight.ru research group. The first to become available was the novel chemical 3-MeO-PCE, sometimes called methoxyeticyclidine by vendors and users. BRC announced 3-MeO-PCE as an 'invite only' chemical on 28 October 2010. The invite only subsection was introduced specifically for 3-MeO-PCE, which was deemed to have a relatively high propensity for behavioural toxicity and psychosis. To place an order, prospective buyers had to contact BRC directly and describe a proposed 'research use' before ordering. Shortly after the BRC release, 3-MeO-PCE was reported to the EMCDDA on 17 November 2010 by the UK.^[173] In addition, a large number of experiences with 3-MeO-PCE describing largely positive dissociative effects with potency slightly lower than PCP began to appear on a number of drug forums including www.bluelight.ru and www.drugs-forum.com. 11 mg of 3-MeO-PCE HCl insufflated induced a strong dissociative state characterized by sensory enhancement, euphoria, analgesia and tactile numbness lasting 3–5 hours.

In April 2011, 3-MeO-PCP was offered in limited quantities by BRC and reports appeared on www.bluelight.ru and other drug forums soon after. 3-MeO-PCP is active via oral, insufflation, inhalation, and injection and is slightly more potent than PCP, exhibiting threshold activity at 3–5 mgs and generally strong dissociative effects at 10–20 mgs. Consistent with earlier posts by the www.bluelight.ru research group, the effects were generally positive. A number of other vendors also offered 3-MeO-PCP.

In September 2011, BRC informed customers that it would offer two novel invite only compounds 3-MeO-PCPy and 3-MeO-PCPr. These materials originally researched by hugo24 and fastandbulbous were absent from the scientific literature at the time. By the end of September, experience reports on 3-MeO-PCPr and 3-MeO-PCPy appear on several drug forums including www.bluelight.ru and www.drugs-forum.com. Both compounds are active, inducing characteristic dissociative intoxication at 5–10 mgs via oral ingestion

and insulfation. Although reports are limited, many users described the effects positively. Following the success of these compounds, additional vendors soon emerged offering 3-MeO-PCP and 3-MeO-PCE.^[160] 3-MeO-PCP was reported to the EMCDDA by the UK on 29 March 2012.^[185] The identity of RC samples of 3-MeO-PCP and 3-MeO-PCE have been confirmed through MS and NMR analysis^[149] and detailed analytical characterization of 4-MeO-PCP, 3-MeO-PCP, 3-MeO-PCPy and several analogues has been published.^[186] 3-MeO-PCP continues to be available from a number of non-UK-based RC vendors as of March 2014.

3-[1-(Ethylamino)cyclohexyl]phenol (3-HO-PCE) and 3-HO-PCP

3-HO-PCP and 3-[1-(ethylamino)cyclohexyl]phenol (3-HO-PCE) have been offered as RCs. While 3-HO-PCP has been extensively researched, 3-HO-PCE was novel. 3-HO-PCP has high affinity for NMDAR as well as MOR affinity.^[166] 3-HO-PCP frequently appears in underground arylcyclohexylamines discussions. Its varying psychoactive effects were described by several www.bluelight.ru members including the www.bluelight.ru research group prior to its availability as an RC around 2009. A post discussing 3-HO-PCE as an RC appeared on www.bluelight.ru in early May 2012. Several reports on Swiss drug forum www.flashback.org exist through 2013.^[187,188] Posts on www.bluelight.ru and www.drugs-forum.com discussing 3-HO-PCE availability as an RC began in July 2012. Some forum members speculated the 3-HO-PCE circulating the market was fake, based on a lack of psychoactivity.^[187] No analytical data on the material sold as 3-HO-PCP or 3-HO-PCE currently exists in the literature and widespread use of these compounds has not occurred.

Aryl-amino-cyclohexan-2-ones revisited: 2-methoxy-ketamine and *N*-ethylketamine

On 20 May 2010, Polish chemist and www.bluelight.ru member, adder, posted a summary on www.bluelight.ru reviewing the psychoactive effects of over 30 arylcyclohexylamine-based dissociatives, stimulants, and opioids he claimed to have synthesized and tested along with several collaborators. Of particular importance were adder's largely positive descriptions of two aryl-amino-cyclohexan-2-ones 2-(2-methoxyphenyl)-2-(methylamino)cyclohexanone (2-MeO-deschloroketamine, 2-MK) and 2-(2-chlorophenyl)-2-(ethylamino)cyclohexan-1-one (*N*-ethylnorketamine, *N*-EK). Calvin Steven's 1963 and 1966 patents described the synthesis of 2-MK and legally covered, but did not specifically describe, MXE and *N*-EK.^[34,189] An interesting part of this story is that some www.bluelight.ru members have questioned the authenticity of this 2010 adder post. Critics cite inconsistencies between doses reported with subsequent findings, the large number of compounds said to be produced in a short period, and the fact that he appears to have been 20 at the time of the post. adder maintains the authenticity, noting he was part of a larger research group a claim which is supported by the original post (adder, pers. comm.). This 'dispute' serves as an example of the potential complications of using information from anonymous Internet sources. Authentic or not, adder's 2010 post has influenced the RC dissociative market.

Prior to the 5 April 2012 temporary ban, MXE had been the only aryl-amino-cyclohexan-2-one sold online aside from ketamine and possibly tiletamine. The MXE ban left a void in the UK

based RC market for ketamine-like dissociatives. The first discussion of 2-MK being offered as an RC appeared on www.bluelight.ru in early February 2012. Sometime in May 2012, BRC offered samples of 2-MK and reports of psychoactive effects soon appeared on www.bluelight.ru and other forms.^[165] Availability of 2-MK increased over the preceding months. Confirming 2-MK availability, unpublished analysis of a white crystalline solid labelled as 2-MK from www.buyanychem.com was consistent with high purity racemic 2-MK (optical rotation, ¹H and ¹³C NMR and GC-MS). A beige crystalline solid marketed as 2-MK was obtained in January 2014 from an European based RC vendor and proved consistent with high purity 2-MK based on GC-MS and ¹H and ¹³C NMR. 2-MK was reported to the EMCDDA by Sweden on 30 August, 2012.^[185] Despite much initial interest and adder's claims, 2-MK proved disappointing to many users; potency was low and effects varied enormously between users.

The first online forum report from a user obtaining an RC sample of *N*-EK appeared on www.bluelight.ru on 7 August 2012. A number of additional posts appeared describing receiving samples of *N*-EK and the psychoactive effects following ingestion.^[190] On 7 September 2012, BRC announced it would be offering *N*-EK stating they could not take credit for the material but that it 'popped up out of the blue'. *N*-EK was offered through several sources and a large number of posts on the psychoactive effects of *N*-EK followed on www.bluelight.ru and www.drugs-forum.com. *N*-EK received mixed reviews, while many described effects positively, often comparing it to ketamine, reduced potency and adverse effects including nose bleeds were reported by others. Misrepresentation may be partially responsible for the inconsistent reports. While *N*-EK was reported to the EMCDDA on 17 September 2012 from the UK,^[185] a sample of *N*-EK supplied to us from a www.bluelight.ru forum member, obtained from a UK vendor, when analyzed was found to be MXE (melting point and GC-MS). A sample consisting of a white powder marketed as *N*-EK obtain in January 2014 from an European based RC vendor proved consistent with high purity *N*-EK based on GC-MS and ¹H and ¹³C NMR. In addition to potential misrepresentation, a number of factors may contribute to the variable responses including purity and inter-subject variability, or a combination of these factors.

In conjunction with the 2012 UK arylcyclohexylamine ban, UK-based RC vendors removed arylcyclohexylamines from their sites. As of February 2014, MXE, 4-MeO-PCP, 3-MeO-PCP, *N*-EK, and 2-MK remain unscheduled in many countries including the USA and are still available as of March 2014 through several non-UK online RC vendors.

The diarylethylamines

The most recent class of dissociatives to emerge on the RC market are the diarylethylamines, which at the time of writing are represented by 1-(1,2-diphenethyl)piperidine (diphenidine) and 1-[1-(2-methoxyphenyl)-2-phenylethyl]piperidine (2-MeO-diphenidine) (Figure 6). The first synthesis of diphenidine was published in 1924 by Christiaen who used a modified Brulyants reaction, similar to the reaction later used by Maddox in the first PCP synthesis.^[191] Since 1924, diphenidine has been the subject of several synthetic and pharmacological investigations.^[191–193] Importantly diphenidine has been shown to act as an NMDAR antagonist^[193] and can be viewed as an MK-801 homeomorph and shares structural features with arylcyclohexylamines. While diphenidine was never used or investigated medically, several related compounds have been

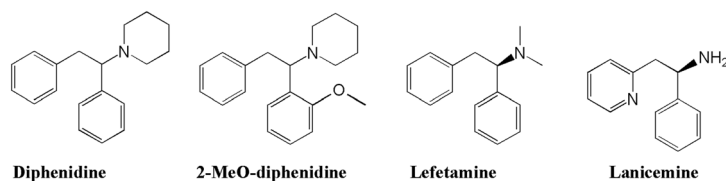


Figure 6. Diarylethylamines used as research chemicals (diphenidine and 2-MeO- diphenidine) and two used clinically (lefetamine and laticemine).

and include the withdrawn analgesic lefetamine and investigational compounds such as AstraZenica's NMDAR antagonist antidepressant Lanicemine, and neurodegenerative disease and anti-epileptic agent Remacemide.^[194]

On 26 February 2013, the UK arylcyclohexylamine ban came into effect. Two weeks after the ban, a member of the forum www.ukchemicalresearch.org stated he received an e-mail from the RC vendor www.chemicalwire.com saying diphenidine was available to 'advanced customers'. In the following weeks various users began posting experiences with diphenidine on a number of forums including www.ukchemicalresearch.org, www.bluelight.ru, and www.drugs-forum.com.^[195] A sample of 'diphenidine powder' and 'diphenidine crystal' were obtained from UK based RC vendor www.discofood.com in January 2014 and were found to be consistent with a reference sample of diphenidine using GC/MS and melting point. Diphenidine users have reported mild effects at doses of 50–100 mg, with strong dissociative effects starting at oral doses of 110 mg and higher doses inducing bizarre somatosensory phenomena and transient anterograde amnesia, lasting 3–6 h.^[196]

With diphenidine's success, it was only a matter of time until additional RC diarylethylamines were marketed. During the initial review phase of this publication, 2-MeO-Diphenidine was first marketed by www.chemicalwire.com as a dissociative RC in late November 2013. On the www.chemicalwire.com product page, 2-MeO-diphenidine is said to be an NMDAR antagonist similar to 'Methoxetamine and Ketamine' but 'also acts on the dopamine transport'. Although it is unknown why 2-MeO-diphenidine was chosen, 2-MeO-Diphenidine is not novel, its synthesis and NMDAR binding affinity are described in a 1989 patent.^[193] Information of the activity of diphenidine or 2-MeO-diphenidine on the dopamine transporter could not be found.

The first 2-MeO-diphenidine-related post, stating it was available from an RC vendor, appeared on www.ukchemicalresearch.org on 23 November 2013 and shortly thereafter posts appeared on www.bluelight.ru.^[197,198] In the short time since, availability from vendors and online forum posts on 2-MeO-diphenidine have steadily increased. A white powder obtained from UK based RC vendor www.discofood.com in January 2014 was consistent with a reference sample of 2-MeO-diphenidine using GC/MS and melting point. Many vendor sites have specifically marketed

diphenidine and 2-MeO-diphenidine as legal replacements for banned arylcyclohexylamines like 4-MeO-PCP and methoxetamine.

2-MeO-diphenidine appears to be slightly more active than diphenidine with dissociative effects beginning at 80 mg. Both compounds show variably in qualitative effects and duration, with higher doses having residual psychoactive effects that can last several days. Users also report a steep dose response curve.^[197,198] Importantly some users have begun to report troubling responses including tachycardia, hyperthermia, and hospitalization due to seizures with higher doses of diphenidine and/or 2-MeO-diphenidine.^[196–198] Although anecdotal, there is some basis in that the related compound lefetamine has been observed to cause seizure in rats.^[199] These adverse responses should be closely monitored for harm-reduction purposes.

Until a generic diarylethylamine ban is implemented, it seems possible additional diarylethylamine-based dissociative RCs will become available. In fact there is suggestion that some vendors have already begun pursuing and actively testing the next generation of diarylethylamines based on online forums and interviews with forum members.

Abuse liability

An area important to the current development of CNS active drugs is abuse liability, i.e. the ability of a drug to produce positive subjective or reinforcing effects which is believed to predict risk of non-medical use or abuse.^[200,201] The factors which determine abuse liability are complex, and can be classified as pharmacological and non-pharmacological. Important pharmacological factors include drug formulation, route of administration, and pharmacokinetic and pharmacodynamic properties of the drug. Non-pharmacological factors include age, socioeconomic status, cultural perspectives, cost, and availability of the drug. For example, DXM usage is more common among teens partially as a result of availability and cost relative to alternatives.^[202] Another example is tiletamine abuse by veterinarians.^[114,203,204] One final example worth looking at is memantine. Despite being available from Internet retailers, non-medical use of memantine has remained rare. In the published reports it appears to be used by curious psychonauts interested in its novelty rather than as a drug of choice or recreation. While reports

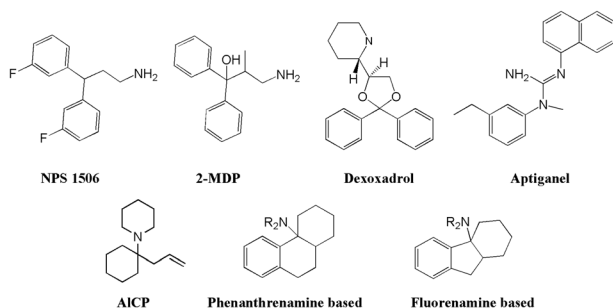


Figure 7. Some known uncompetitive NMDAR antagonists with potential to serve as structural leads to future RC dissociatives.

from users of memantine generally related the subjective effects as positive, the long duration of action (> 40 h) was stated to be undesirable by many users.^[153,154] In the case of memantine, the combination of the longer half-life with availability of more desirable alternatives likely contribute to the current limited non-medical use.

Abuse liability of NMDAR antagonists has been discussed by FDA staff^[205] and others.^[200] Carrol has reviewed research on abuse liability of PCP and related compounds including pre-clinical animal models such as drug discrimination, self-administration, tolerance, and physical dependence.^[206] While a number of uncompetitive NMDAR antagonists including aptiganel, remacemide, and gacyclidine, have been stated to have reduced PCP-like effects in pre-clinical trials subsequent clinical evaluation showed dissociative activity.^[4,146,207] Some promise has however been observed with glycine site-competitive antagonists such as 1-aminocyclopropanecarboxylic acid (ACPC) in preclinical and clinical evaluations.^[4] Non-competitive allosteric antagonists targeting NR2B subunit containing NMDARs including ifenprodil and eliprodil have also been reported to exhibit reduced PCP like effects in animals and humans.^[4] Thus targeting specific sub-units of the NMDAR channel may be a strategy to reduce dissociative effects and limit abuse liability. However, as NMDAR antagonism appears involved in both therapeutic and dissociative effects, it is unclear what effect a reduced abuse potential will have on the therapeutic activity. Legitimate medical users must be considered, and should not be penalized due to non-medical use/abuse which is likely to continue despite legislative and regulatory efforts or medical advancements in abuse liability.

Conclusion

Early scientific and medical research with dissociative agents occurred in a pre-Internet era; likewise the first clandestine arylcyclohexylamine chemists operated without easily accessible synthetic and pharmacological information now facilitated by the Internet. Still many early clandestine chemists clearly accessed the existing arylcyclohexylamines literature for inspiration and synthetic knowledge. This is exemplified by the fact that despite being commonly called designer drugs, all but one of the 14 pre-2000 analogues reviewed were first reported in the scientific literature (Figure 3). While PCP remains readily available in numerous US cities, street analogues have virtually disappeared with no reports found after the 1990s. It is noteworthy that in the late 1990s as arylcyclohexylamines began to disappear from the streets, various dissociatives began to be traded on the Internet.

While ketamine and DXM were offered for a time via gray-market sources, the modern dissociative RC market began in 2008. Starting with 4-MeO-PCP, the dissociative RC market has rapidly evolved in four years to encompass at least a dozen dissociatives. Impressively, half of these dissociatives are novel, and their origins can be traced to a handful of influential members of *The Hive* or *www.bluelight.ru* drug forums. One of these novel RCs, methoxetamine, is a rare instance of a true designer drug, rationally designed for the gray-market based on a combination of scientific and folk pharmacology principles. Accordingly, MXE has become emblematic of underground drug development in the Internet age and a unique insight into the factors that allow these markets to evolve. While many see little benefit to the RC market in some cases scientific and medical uses can evolve out of these agents. For example, despite misuses, MXE and 4-MeO-PCP have been proposed for therapeutic and research applications that may be realized in the future.^[208,209]

While the UK generic arylcyclohexylamine ban and to a lesser extent similar laws in the USA cover many simple arylcyclohexylamines, many laws fail to cover more conformationally restricted derivatives, a large number of which have been described in the scientific literature. Examples include such classes as the phenanthrenamine and fluorenamine-based NMDAR antagonists. Likewise, the UK arylcyclohexylamine ban fails to cover derivatives in which the aromatic ring is replaced with aliphatic chain substituents. The allyl and propargyl derivatives, 1-[1-(prop-2-en-1-yl)cyclohexyl]piperidine (AICP) and 1-(1-ethynylcyclohexyl)piperidine (PrCP) have been described as active in the literature (Figure 7).^[210] In addition, non-aryl cyclohexylamine based uncompetitive NMDAR antagonists based on diphenidine, dexodrol, 2-MDP, aptiganel, or NPS 1506 (Figures 6 and 7) could become future RC dissociatives. Supporting this psychoactive dissociative effects of dexodrol, aptiganel and 2-MDP have already been described on online drug forums. While these classes could themselves be scheduled, a demand exists and newer classes will almost certainly take the place of those banned. It must be considered that generic bans tend to have the unintentional consequence of adversely impacting scientific and medical research. Generic bans will likely continue to be ineffective as clandestine chemists and the new breed of RC vendors have a well established history of skirting legislative roadblocks. The fact that diphenidine was available on the RC market only weeks after the UK arylcyclohexylamine ban exemplifies both the resilience of these markets and the ineffectiveness of current legal strategies.

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