

A new trend in drugs-of-abuse; the 2C-series of phenethylamine designer drugs

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Key words

2C-B, 2C-T-2, 2C-T-7
Designer drugs-of-abuse
Ecstasy
Smartdrug
Smartshop

Abstract

Objective: To collect data related to phenethylamine drugs-of-abuse of the 2C-series, to review possible health risks of their use and to discuss legal counter actions of authorities in the European Union (EU).

Settings: Dutch smartshops.

Methods: In the period of 1994–2002, all products that were claimed to contain synthetic drugs and sold in the smartshops, were purchased. The contents were analysed using analytical chemical technologies such as gas chromatography/mass spectrometry and nuclear magnetic resonance. Additionally, using computerised searches in relevant databases and checking cross-references, literature and documents were screened for scientific based information.

Results: All purchased products proved to be tablets, of which most of them contained one of the phenethylamine designer drugs 2C-B, 2C-T-2 or 2C-T-7. The different drugs were introduced on the Dutch smartshop market within time intervals of approximately three years. The information that was supplied on leaflets and accompanied the products sometimes appeared to be extensive, but was partly misleading and incorrect. Besides that, scientific based information in respect to health risks of drugs of the 2C-series and the detection of their abuse was scarce. Until now no intoxications have been reported in the EU and no centralised legal actions have been taken to prevent possible intoxications.

Conclusions: The lack of observed intoxications may justify the absence of legal actions in the EU against phenethylamine designer drugs-of-abuse of the 2C-series. However, this may also be explained by either the inability of toxicologists to detect the abuse of substances of the 2C-series or the unawareness of the phenomenon of these drugs. Therefore, EU authorities should promote the availability of relevant standards, validated assays and scientific knowledge regarding these drugs.

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Introduction

The frequent appearance of phenethylamine designer drugs as drugs-of-abuse is a matter of concern for all authorities involved. Historically, this problem already started in the late eighties with the introduction of 'Ecstasy', better known as MDMA (Table 1)¹. Its inclusion in anti-drug legislation shifted the problem as MDMA was followed by several other phenethylamine drugs such as MDA, MDEA, MDOH, MBDB, BDB, 4-MTA and 4-PMMA (Table 1). New phenethylamine drugs are being introduced because these compounds are not covered by existing legislation. Therefore, the new

drugs can not be considered as illicit drugs until their names are implemented. As a consequence, prompt legal action directed against their production, marketing and consumption is not easy to organise. Occasionally, a less new phenethylamine drug undergoes a revival, e.g., DOB and 4-PMA (Table 1).

For this study, we collected data related to the phenomenon of phenethylamine designer drugs on the Dutch smartdrug market. This market consists of a commercial network of so-called smartshops. The definition of a smartdrug in this context is broad and covers 'magic' mushrooms, herbal preparations containing psychoactive substances, and nutritional supplements such as creatine among others. Unfortunately, no special legislation and regulation exists which controls the smartshops and therefore special attention should be paid to this smartdrug trade. Here, we describe the development of a trend of drugs-of-abuse belonging to the so-called series 2C-series of phenethylamine designer drugs. Drugs in this series have the 2,5-dimethoxyphenethylamine backbone in common, which enables their binding to 5-HT₂ receptors⁷. These drugs are very potent and cause hallucinations⁸.

Methods

Products that were claimed to contain synthetic drugs and sold in smartshops, were purchased in the period of 1994–2002 from shops all over the country. Shops in the central region of the Netherlands ('Randstad') were visited at least twice a year during the period of investigation. The selection of these shops was performed randomly, while the number of shops visited varied with time. Shops in other parts of the country were selected based on informal information that synthetic drugs were available and were visited when it was considered appropriate.

After a preliminary analytical screening (enzyme-multiple immunoassay [EMIT®] amphetamine-like immunoassay, thin layer chromatography [TLC] and/or gas chromatography/nitrogen phosphorous detector [GC/NPD]), those products that were suspected for the presence of phenethylamine designer drugs (positive immunoassay result, suspected TLC spot or GC/NPD peak) were analysed by analytical toxicological methodologies based on gas chromatography/mass spectrometry (GC/MS)^{9, 10}. In each case, final identification was established once more by GC/MS as well as by comparing the analytical results with those of a reference standard. Non-certified reference standards were verified by nuclear magnetic resonance (NMR). If necessary, the reference standard was synthesised and verified by NMR amongst others. The written information supplied with the drug was also evaluated.

Results and discussion

Identified compounds

A total number of 12 shops were visited, of which 7 were located in the central region of the Netherlands. Five different products were identified as being of interest and purchased subsequently (Table 2). All of these products were available in the central region, while some of them were only obtainable elsewhere. Every product consisted of tablets and contained a synthetic substance. Four different substances were identified, three of them belonging to the 2C-series of phenethylamine designer drugs. These drugs of the 2C-series appeared on the market within a time interval of three years. The other substance found was 4-MTA, an amphetamine-like compound, which appearance was reported and discussed elsewhere^{3, 11}. Together with the purchased products, the shops gave some incorrect information. In the supplied information of one product for example no drugs were mentioned, while of another product the correct drug name was not given.

The first drug identified from the 2C-series was 4-bromo-2,5-dimethoxyphenethylamine (2C-B)⁹. It was only available in smartshops for a short period during which its popularity increased quickly. This development stopped when the Dutch authorities scheduled 2C-B provisionally on the list of narcotic and psychotropic substances with unacceptable risks. Such an action should always be followed by a final registration in the respective law, however this second step was not carried out within the legal time frame. Therefore, the marketing and consumption of 2C-B is not a criminal action at this moment. 2C-B, however, did not re-enter the smartshops. In order to protect their image, some shops decided to formulate quality recommendations, which included the termination of the marketing of 2C-B.

Nevertheless, 2C-B was succeeded on the smart-drug market by 4-ethylthio-2,5-dimethoxyphenethylamine (2C-T-2)^{3, 10}. At first 2C-T-2 was marketed under incorrect names, but later it became available under its correct name (Table 2). The products were supplied with a leaflet containing simple information. In this case, the Dutch authorities stopped the distribution based on an Act that stated that pharmaceutical

substances should only be available in pharmacies after an official registration procedure. Therefore, the marketing of 2C-T-2 was and is considered to be an economical crime and smartshops no longer market the drug. From that time on, the same Act also regulated 2C-B.

In the year 2000, we detected that 4-propylthio-2,5-dimethoxyphenethylamine (2C-T-7) was being sold in smartshops. The leaflet provided with the product seemed to contain extensive information, although some of it was misleading. For example, it was stated that 2C-T-7 is a dietary supplement, which it is certainly not. Although it was not clear which kind of action the Dutch authorities took, it was observed that after some months 2C-T-7 disappeared from the market. It is likely that, the Act that regulated 2C-T-2 and 2C-B was also applied on 2C-T-7.

Health risks of the 2C-series

Only limited information is available in respect to health risks and use of phenethylamine designer drugs of the 2C-series. Preliminary test reports with 2C-B, 2C-T-2 and 2C-T-7 indicated minimal physical symptoms when administered orally in the range of approximately 10 to 30 mg^{7, 12}. A review on structure-activity relationships suggested that in this dose range the relative potency of the mentioned drugs was 15–16 times that of mescaline¹³. However, these studies were based on self-reports of persons under influence. Claims that these types of drugs are promising as facilitators in psychotherapy¹² are difficult to verify, because the existing drug laws discourage such studies of investigation¹⁴. The relationships between dose, effects, way of administration and intoxication are therefore still inconclusive.

It should be realised that possible health risks may depend on the kind of potential users and their behaviour. The group for example, that is interested in MDMA and 'dance rave', 'techno', or 'acid-house' parties, risks to ingest 2C-B involuntary as 2C-B may be a contaminant in 'ecstasy' tablets^{9, 15}. While expecting MDMA-like effects, such users could experience unexpectedly frightening hallucinations. Moreover, the possible negative influence on driving performance after parties should also be considered⁹.

Table 1 Phenethylamine designer drugs that were introduced on the drugs-of-abuse market after MDMA

Name of drug	Full name	Literature reference	Estimated year of first appearance in the Netherlands
MDMA	3,4-methylenedioxyamphetamine	1	1985
MDA	3,4-methylenedioxyamphetamine	1	1985
MDEA	3,4-methylenedioxyethylamphetamine	1	1990
MDOH	N-hydroxy-3,4-methylenedioxyamphetamine	1	1995
MBDB	N-methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine	2	1995
BDB	1-(1,3-benzodioxol-5-yl)-2-butanamine	2	1995
4-MTA	para-methylthioamphetamine	3	1997
4-PMMA	para-methoxymetamphetamine	4	Unknown
DOB	4-bromo-2,5-dimethoxyamphetamine	5	Revival
4-PMA	para-methoxyamphetamine	6	2000
4-PMA	para-methoxyamphetamine	6	2000

Another group of users is merely interested in the hallucinogenic effects of phenethylamine drugs of the 2C-series in a quite and friendly environment. They are in principal better informed and prepared, but could be misled by incorrect information as observed in this investigation and elsewhere^{3, 16}. Unfortunately, these users may try higher doses as well as more risky ways of administration such as snorting and insufflation. Of the three deaths associated for instance with 2C-T-7¹⁷, two of them are supposed to have insufflated the drug.

Policy of the European Union

In Europe, national authorities have different policies on drugs. In order to harmonise drug issues, the European Union (EU) created the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). This centre was set up to provide objective, reliable and comparable information concerning drugs and drug addiction and their consequences. In addition, the EMCDDA co-ordinates and carries out work related to new synthetic drugs. This network provides the EU with an early-warning system that can identify new drugs as they appear on the European market. This system proved its effectiveness as the above-mentioned examples of the 2C-series designer drugs have been discovered promptly. The EMCDDA also claims to have detected another member of the 2C-series, namely 2C-T-5 (4-cyclohexylthio-2,5-dimethoxyphenethylamine), although not documented scientifically until now¹⁸.

Up to now the EU policy resulted in a consensus that the health risks of the abuse of some phenethylamine designer drugs are significant, e.g., MDMA, MDA, MDOH, MDEA, 4-MTA, 4-PMA and 4-PMMA. Consequently, these drugs are forbidden in all EU member countries^{4, 16}. For MBDB and BDB, despite some serious concerns regarding MBDB¹⁹, such a consensus does not exist and therefore their use is still not forbidden in some member countries²⁰. In respect to the 2C-series of phenethylamine designer drugs, the EMCDDA did not take any formal action.

Compared to Europe the phenomenon of the 2C-series of phenethylamine designer drugs in the USA already has a longer history. The Drug Enforcement Administration (DEA) encountered 2C-B for the first time in the late seventies and in 1995 it became a Schedule I substance in the USA, making it illegal to market or

possess without a proper license¹⁷. Very recently, the DEA temporarily placed also 2C-T-7 in Schedule I. This so-called emergency scheduling is presumably the result of the fact that the three deaths have been linked with the use of 2C-T-7^{21, 22}.

In Europe there have been no reports of case studies of intoxications associated with the drugs of the 2C-series and this may justify the absence of formal actions by the EU. However, the lack of adequate reference standards, analytical assays, and knowledge about the metabolism suggest that it can be seriously doubted if toxicologists in general are able to monitor such intoxications. As far as known the analytical information to identify the drugs of the C-series is mainly circulating within forensic chemistry and to some extent within forensic toxicology^{16, 23–25}. Only for 2C-B some experiments in biological specimens and data of metabolites are available^{26, 27}. Therefore, relevant EU authorities should promote the availability of relevant standards, validated assays and scientific knowledge. The EU should not rely on national legislation and risk overdose problems as also seen in the past with drugs of the D-series (e.g., 4-bromo-2,5-dimethoxyamphetamine [DOB] and 4-methyl-2,5-dimethoxyamphetamine [DOM])⁷.

In contradiction to the legal status of the 2C-series, an European prohibition consensus does exist for drugs of the D-series of phenethylamine designer drugs, meaning that the manufacturing and selling of these drugs is forbidden without an appropriate license. The United Nations (UN), however, have initiated this consensus as the respective drugs of the D-series are on the list of the UN Convention of Psychotropic Substances of 1971. This convention controls the international traffic and trade of psychotropic compounds and obliges participating governments to regulate these drugs on a national level. The very recent inclusion of 2C-B in this convention may stimulate the EU authorities to re-evaluate critically the potential dangers of the 2C-series of phenethylamine designer drugs.

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Table 2 *Supplied information and actual contents of products containing designer drugs of the 2C-series*

<i>Name of product</i>	<i>Year of first appearance in the Netherlands</i>	<i>Supplied written information</i>	<i>Claimed dosage</i>	<i>Actual content</i>	<i>Price per tablet (€)</i>
2C-B	1994	None	5 mg of 2C-B	2C-B	Unknown
S-5 (synthetic herbs)	1997	Very limited information on the packing in Dutch	None	2C-T-2	11.34
2C-T-7	1997	Simple information on leaflet in Dutch	8 mg of 2C-T-7	2C-T-2	5.67
2C-T-2	1997	Simple information on leaflet in Dutch	8 mg of 2C-T-2	2C-T-2	3.78–10.21
Blue Mystics	2000	Extensive information on leaflet in Dutch and in English	10 mg of 2C-T-7	2C-T-7	3.78–6.81

fication of 2C-T-2 and C.S. Martins, I.J. Póvoa and C.A. Salgueiro for the final identification of 2C-T-2 as well as 2C-T-7.

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