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Chapter 6

Instability of the ecstasy market and a new kid on the block: mephedrone



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Abstract

Recently, several reports have indicated instability of the ecstasy market in The Netherlands and other EU countries. In the current study, we demonstrate this instability in The Netherlands, showing a decrease of ecstasy tablets containing MDMA (3,4-methylenedioxymetamphetamine) by more than 50% in 2009. In addition, we describe a partial replacement of MDMA in tablets sold as ecstasy by a previously unseen substance, mephedrone (or 4-methylmethcathinone). Mephedrone was quantified and ecstasy tablets contained between 96 and 155 milligrams of this new compound. So far, no studies about mephedrone's effects have been published. For this study, we gathered information on the acute subjective effects of mephedrone from 70 regular ecstasy users. Overall, the majority of users considered the effects enjoyable. Mephedrone seemed to evoke effects similar to other amphetamine-type psychostimulants, including MDMA. In contrast to MDMA, however, mephedrone induced strong feelings of craving in most users. If the unstable ecstasy market situation persists, the potential of mephedrone to substitute for MDMA might be substantial. Mephedrone, sold as ecstasy, is therefore likely to be a valid cause for health concern.

Introduction

The market of illicit drugs can be considered just as dynamic as markets for legal products. For a variety of reasons, new synthetic drugs, surnamed designer drugs, are continuously appearing on the illicit drug market; if a new drug shows interesting marketing potential, if it's not yet under a controlled substance act and/or if an established drug has become scarcer as a result of increased drug enforcement activities (Jerrard, 1990; Wodak, 2008). Over the past two years there have been reports on a shortage of MDMA in the ecstasy market in The Netherlands and other EU countries, probably resulting from increasingly successful efforts to prevent the diversion of precursors to manufacture MDMA, such as piperonylmethylketone (PMK) (EMCDDA, 2009). At the same time, previously unseen substances on the illicit drug market were reported by

the European Early Warning System (EWS), such as substituted piperazines, N-methylated cathinones and halogenated amphetamine derivatives among other chemical classes. Some of these substances were categorized as designer drugs, intended to replace MDMA in ecstasy tablets.

New designer drugs usually display characteristics similar to already popular and established illicit drugs. Often they are just chemically modified at a single position of the original molecule. For instance, MDA, MDMA and MDEA (commonly sold as ecstasy) are commonly referred to as designer drugs of the amphetamine-type (Maurer, *et al.*, 2004), also called phenylethylamines. But a whole range of new designer drugs is emerging. For instance, methcathinone was launched into the recreational drug market after the increased criminalization of ecstasy (Sparago, *et al.*, 1996; Dal Cason, *et al.*, 1997; Hegadoren, *et al.*, 1999). Methylone (3,4-methylenedioxy-*N*-methylcathinone) and mCPP (meta-chlorophenyl-piperazine) were previously described as serotonergic substitutes for ecstasy (Bossong, *et al.*, 2005). Whether these designer drugs are suitable alternatives from the consumer's health perspective, in terms of effects or even toxicology often remains to be investigated however.

The Drug Information and Monitoring System (DIMS) in The Netherlands is a toxicoepidemiologic monitor of illegal drug markets and one of its objectives is to identify trends and new substances circulating on the drug market from the perspective of health care (Bossong, *et al.*, 2009). In this article, we aim to describe the recent instability of the ecstasy market and investigate whether this has led to the introduction of new designer drugs to the market and their possible health risks.

Methods

Drug samples

All DIMS drug samples were collected according to the methods described by Vogels *et al.* (2009). In the current study, 12,331 ecstasy tablets were

analysed over the period 2008-2009 from individual consumers using the DIMS system. We used data on tablets sold as ecstasy (MDMA) to describe the instability of the ecstasy market. Secondly, we describe the rise of the main identified new substance on the Dutch synthetic drug market: mephedrone (4-methylmethcathinone, shortly 4-MMC, 'meow meow' or MMCAT). Data from The Netherlands Forensic Institute (NFI) were used to confirm the rise of this substance. The NFI illicit drug samples were obtained by police seizures. All samples were received at The Netherlands Forensic Institute during the year 2009.

Laboratory analysis

Identification of mephedrone was done by The Netherlands Forensic Institute (NFI). For identification electron impact (EI) mass spectra were obtained using an Agilent 6890 gas chromatograph equipped with an Agilent 5973 Mass Selective Detector (MSD) and an Agilent G2614 autosampler. Helium was used as the carrier gas at a constant flow rate of 1.0 mL/min. An Agilent Ultra-1 12 m x 0.20 mm x 0.33 μ m column was used with an oven temperature program from 110°C (1 min hold) with 40°C/min to 300°C (2.75 min hold); the injector temperature was 275°C and the MSD interface was set at 280°C. The standard split/ splitless liner was used in split injection mode (1:50).

Quantitative analysis of mephedrone was performed using an Agilent 6890 gas chromatograph equipped with Flame Ionisation detector (FID) and an Agilent G2614 autosampler. Nitrogen was used as the carrier gas at a constant flow rate of 1.6 ml/min. An Agilent Ultra-1 25 m x 0.32 mm x 0.52 μ m column was used with an oven temperature program from 175°C (5 min hold) with 10°C/min to 280°C (0 min hold); the injector and detector temperatures were 275°C and 300°C, respectively. The standard split/ splitless liner was used in split injection mode (1:25). From ground and homogenised tablet mass an alkaline extract was made using hexane with C20 as internal standard. Certified reference mephedrone was obtained by the NFI from the National Measurement Institute (Pymble NSW, Australia).

Acute subjective effects

We obtained descriptions of the acute subjective effects of mephedrone from regular ecstasy users through the DIMS network and through the peer-led intervention network Unity. An information request was put to all members of the DIMS network, asking users specifically about their previous experiences with the drug sample they handed in. It takes about one week before the person who has his sample tested gets the result from the laboratory, which means that these drug users were not aware of the chemical contents of their drug samples when they provided information on their experience with the drug they handed in for analysis. In addition, we obtained descriptions of the acute subjective effects of mephedrone from users through the Unity-network: a peer led intervention that is part of a national Dutch 'safer dancing' policy, a prevention mix of education, support facilities and juridical measures. Unity attends over 40 festivals and dance events per year. We collected acute subjective effects from June 2009 until December 2009.

Results

Instability of the ecstasy market and mephedrone

Starting from July 2008 the ecstasy market changed quite drastically. From being a fairly stable market for years with more than 90% of the ecstasy tablets containing mainly MDMA (for an overview of the Dutch ecstasy market, see Vogels, *et al.*, 2009), the market became diluted from the second half of 2008 on, leading to less than 50% of ecstasy tablets containing MDMA in the first half of 2009 (Figure 1). The lack of MDMA in ecstasy tablets was mainly compensated for by mCPP (ranging between 23% and 54% in all ecstasy tablets from 2008 to 2009). Other previously described substances were: amphetamine (50 tablets), methamphetamine (40 tablets), caffeine (in more than 500 tablets) and 2C-B (34 tablets). Besides these typically encountered substances on the Dutch ecstasy market some previously unseen pharmacologically active components started to emerge during 2008 and 2009: 4-fluoroamphetamine (25

tablets), ketamine (10 tablets), N-formylamphetamine (16 tablets), 1-(4-Fluorophenyl)piperazine or *p*FPP (6 tablets), metoclopramide (15 tablets) and domperidone (46 tablets). The latter two are medicines and suspected to be added to tablets containing mCPP to suppress the nausea often experienced with that substance.

By far, the most prevalent new compound we found during this period was mephedrone. Mephedrone, misleadingly sold by the dealer as ecstasy, was increasingly detected during 2009 (Figure 1). At the DIMS system, 995 tablets were handed in, representing 11.5% of the total amount ecstasy tablets in 2009. These tablets exclusively contained mephedrone as pharmacologically active substance. DIMS findings were confirmed by police seizures during the same period (more than 100 seizures reported). Based on 21 tablets analysed from different seizures, the quantity of mephedrone base ranged between 96 and 155 milligrams per tablet. Mephedrone was the first and, so far, only cathinone derivative found in tablets sold as ecstasy in The Netherlands.

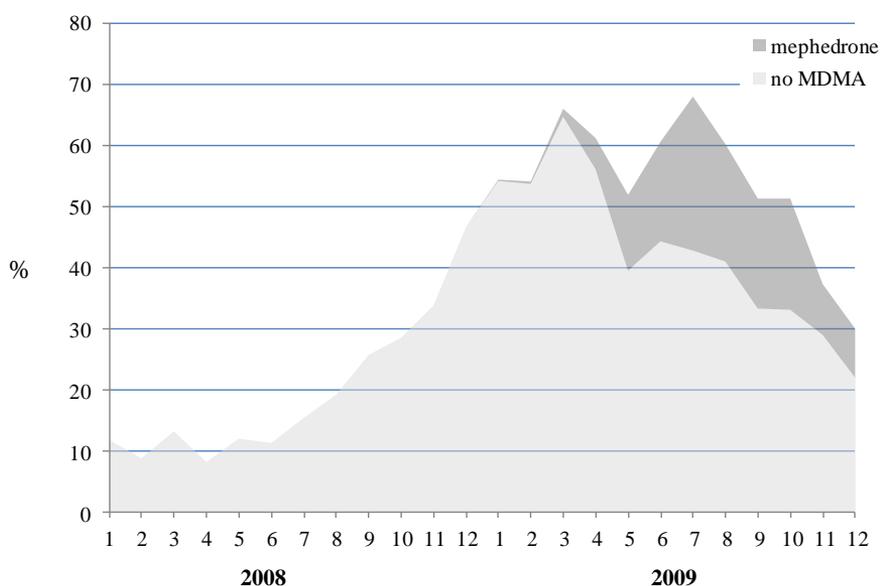


Figure 1. Dilution of the ecstasy market throughout 2008 and 2009, expressed as percentage of tablets not containing MDMA measured per month (total shaded area), the percentage of mephedrone tablets therein is darkly shaded.

Acute subjective effects of mephedrone

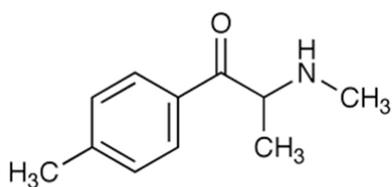
In order to gain some information concerning the effects of mephedrone, we collected information on the acute subjective effects of mephedrone from 70 recreational drug consumers. Most of these users were regular ecstasy users (n=63). The others (n=7) were experimental users, deliberately searching for mephedrone as a novel substance. The reported effects are summarized in Table 1. The contents of tablets of 43 users could be traced back from the quantitative laboratory results and contained between 111 and 120 mg of mephedrone base per tablet. Most effects were reported after ingestion of a single tablet. Information reported by the remaining 27 users broadly indicated similar dosages, but confirmation of this was lacking. The most frequently reported emotional effects were euphoria, talkativeness, improved mood and craving (often reported as the compulsive urge to redose). The most frequently described somatic effects were increased energy and accelerated heartbeat. Most users experienced the overall mephedrone effects as enjoyable and were considering using the substance if the opportunity were to occur again.

Discussion

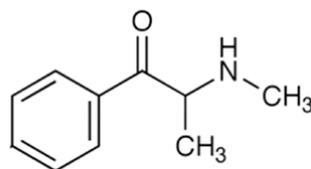
What we describe here is the emergence of a new synthetic drug of the amphetamine-type in the context of an unstable synthetic drug market. Whereas new designer drugs keep emerging regularly, we want to emphasize that in the present report we might have revealed a more causative relation between the situation on the ecstasy market and the rise of novel compounds. Recently others have also hinted at this possibility (Measham, *et al.*, 2010). Producers of illicit drugs may consider a switch to these novel compounds, if the situation with regard to MDMA does not change. A worrying phenomenon is that some new designer drugs, like methcathinone, have been reported to be synthesized in the home environment, made from readily available pharmaceuticals like ephedrine or pseudoephedrine (Belhadj-Tahar and Sadeg, 2005). The unprofessional nature of this manner of drug synthesis could be associated with additional health risks (Stephens, *et al.*, 2008).

Table 1. Most frequently reported acute subjective effects by 70 drug consumers that have tried mephedrone tablets.

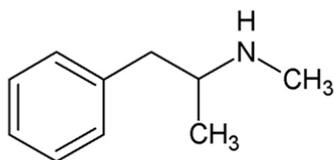
Emotional (<i>n</i>)	Somatic (<i>n</i>)
Increased alertness, more focused (28)	Increased energy, hyperactivity (56)
Euphoria, excitement, improved mood (63)	Dizziness (17)
Urge to talk, openness in communication (51)	Distorted vision, restless eye movements (33)
Craving for the drug (61)	Hyperthermia, warm all over (24)
Depressed, feeling down or sad (11)	Nausea, feeling sick (20)
Anxiety, panicky or nervous (19)	Accelerated heart/heartbeat, tachycardia (44)
	Loss of appetite (29)
	Bruxism, jaw clenching (26)
	Disturbed sleep-pattern (33)
	Low energy, exhaustion, lethargy (23)
<i>Overall experience: pleasant, enjoyable</i>	58
<i>Overall experience: unpleasant, undesirable</i>	12



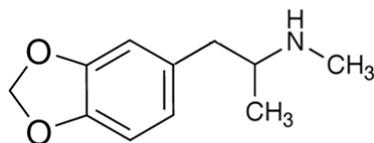
A



B



C



D

Figure 2. Chemical structure of: mephedrone (a), methcathinone (b), methamphetamine (c) and 3,4-methylenedioxyamphetamine (MDMA) (d).

The Psychonaut Research Project, an EU organisation that searches the internet for information regarding new drugs, first identified mephedrone in 2008 (for the Psychonaut Project, see Schifano *et al.*, 2003). The drug first became available in Europe in 2007. The drug was sold as Neodove pills, by the legal high company Neorganics (based in Israel), but this was discontinued in 2008 after Israel made mephedrone illegal (BBC news, 2009). Mephedrone has thus far been reported as having been sold as ecstasy in Australia, Europe and the United States (EMCDDA, 2008).

An advantage for producers of mephedrone is that it is not yet under the scheduled substances act in the Netherlands. Furthermore, mephedrone is available by simply clicking on the internet (BBC news, 2009). Mephedrone supply seems to be dominated worldwide by laboratories situated in China and most EU webshops indicate to order their stocks there. It seems to be sold as a plant fertilizer through various websites. Currently, the EMCDDA and Europol are working on a joint report on mephedrone, which may lead to a formal risk assessment procedure on the substance (EMCDDA, 2010). A similar trajectory has recently been followed for benzylpiperazine (BZP), also sold as 'ecstasy' in tablets, and resulting in legal control measures for this substance in 17 EU Member States (EMCDDA, 2009). Although this is certainly a strong collective effort for prevention, it seems that drug producers are already trying to circumvent the law by offering other 'legal' substituted piperazines through various online webshops. This underlines the difficulties in targeting this relatively new and rapidly shifting designer drug market.

Concerning the subjective effects of mephedrone, there are some exploratory sources from the United Kingdom. They reflect many similar, but not all, acute subjective effects we have found in the current study. For instance, the Lifeline Project has described side-effects, like nose bleeds, nose burns, hallucinations, blood circulation problems, rashes, anxiety, paranoia, fits and delusions (Newcombe, 2009; Measham, *et al.*, 2010). The results of an online poll carried out by the National Addiction Centre among 2,222 readers of a clubbing magazine showed further indications of negative side-effects of mephedrone: headaches (51%), heart palpitations (43%), nausea (27%) and cold or blue fingers (15%) (Dick and Torrance,

2010). One of the possible explanations for some of the differences in effects between these studies and our study could lie in the fact that mephedrone was exclusively taken orally in tablet form by the Dutch drug users, whereas in the United Kingdom, also the intranasal route of administration has been frequently reported.

Mephedrone is structurally closely related to cathinone and methcathinone (for molecular structures, see Figure 2), which are structural analogues of amphetamine and methamphetamine respectively (Sparago, *et al.*, 1996; Gygi, *et al.*, 1996; Dal Cason, *et al.*, 1997). As of yet, very little about mephedrone has been described in scientific literature. Based on our study, it is a psychostimulant with similar properties to MDMA (for MDMA, see the meta-review on acute subjective effects by Baylen and Rosenberg, 2006). But it also differs in some aspects, with perhaps as most striking difference the craving experienced by the drug users with mephedrone, whereas this has rarely been described for MDMA (Huxster, *et al.*, 2006; Baylen and Rosenberg, 2006). This interesting difference might point towards mephedrone inducing a more potent dopaminergic- (DA) relative to serotonergic (5-HT) response in the CNS: it has been postulated that the addictive potential of a drug is lowered if the 5-HT releasing potency relative to DA is higher (Rothman, *et al.*, 2008). For its analogue, methcathinone, chronic use has been described to result in drug dependence (Goldstone, 1993; Calkins, *et al.*, 1995). An alternative explanation for the induced craving by mephedrone could be the relatively short biological half-life of the compound.

Regarding (neuro-)toxicity, we can only refer to compounds with a high structural similarity such as methcathinone. A number of studies have reported acute toxicity of methcathinone (Sparago, *et al.*, 1996; McCann, *et al.*, 1998; Cozzi and Foley, 2003) showing CNS neurotoxicity to 5-HT and DA neurons; persistent reductions in dopamine transporter (DAT) density were found in abstinent methcathinone users, indicative of a loss of DAT or DA terminals (McCann, *et al.*, 1998). Its toxic effects on the DA system have repeatedly been linked to Parkinsonism observed in methcathinone abusers, although this was ascribed to manganese, formed in the synthesis of methcathinone (Sikk, *et al.*, 2007; Stephens, *et al.*, 2008;

Varlibas, *et al.*, 2009). Anyway, extreme caution is needed when inferring similar toxicology to mephedrone. Clearly, experimental research into this subject is needed.

In conclusion, the acute subjective effects we described in this study provide some insight into the mechanism of action of mephedrone and its potential as a substitute for ecstasy. Notwithstanding the neurotoxic effects of MDMA, sold as ecstasy, mephedrone is a valid cause for health concern. It appears a more addictive substance and may otherwise resemble dangerous analogues, such as methcathinone or methamphetamine. It remains unclear whether the situation on the ecstasy market is temporary or more sustained (EMCDDA, 2009). If the unstable synthetic market situation persists, the potential of mephedrone to replace MDMA in ecstasy tablets might be substantial. The present rise of this new designer drug could therefore prove to be more hazardous than in previous instances, when the MDMA market could otherwise be considered to be stable.